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PHYSIOLOGICAL REVIEWS

VOL. III APRIL, 1923 No. 2

VOLUME CHANGES OF THE HEART

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The stroke volume of the heart is probably both for physiological and clinical purposes the most important quantitative function of the whole body. It is much more important than the exact amount of arterial pressure, for the amplitude of the heart's volume change at each beat multiplied by the pulse rate gives the volume of arterial blood supplied to the entire body. Indeed it is particularly from this aspect that at the present time the problem is assuming an importance which is becoming imperative in relation to questions of the oxygen supply of the body, the blood gases, and the coördination of the circulation with respiration during muscular work (Bainbridge), in conditions of asphyxia, and in disease.

Three hundred years ago Harvey solved qualitatively the problem of the volume changes of the heart when he showed that the ventricles are dilated during diastole by the blood returning through the veins. As he saw it, this blood is forced by the contraction of the auricles into the ventricles, and is in turn discharged by them during systole. Harvey scarcely attempted, however, except in the roughest fashion, to determine in quantitative terms the exact volume of blood discharged at each beat. In spite of many investigations devoted to this end in modern times, our textbooks still contain merely qualitative information; and this problem is only now approaching quantitative solution. We do indeed know much regarding the mechanism of the heart, but the coördination and correlation of this organ's behavior with all the other functions of the organism acting as a whole, are still a matter of gaps, guesses, and possibly error.

By analogy with respiration it might be supposed that the heart's tidal volume at a beat is a widely variable quantity. Certainly any one who compares his own sensations when the heart is beating quietly, and when it is pounding in his chest after vigorous muscular work, such as a run, gains this impression. Sketched in its main outlines, respiration behaves as follows: The rate varies from about 15 per minute at rest, up to 40 or more per minute during exercise. Its amplitude varies from 300 or 500 cc. up to four or five times as large volumes of tidal air. In an athelete with increasing exercise it is usually the amplitude of the breaths which alone increases at first; the rate accelerating only after a maximal or nearly maximal amplitude is reached. Within wide limits also the volume of air breathed is such that the oxygen deficit and CO_2 content of the expired air are each about 4 per cent; indicating that in general the total volume of breathing is directly, if roughly, proportional to the oxygen consumption and energy expenditure of the body. This proportionality holds even more exactly of the pulmonary ventilation, for its variations consist, as Haldane and Priestley showed, of variations in the amount of alveolar air of nearly uniform CO_2 content replaced by fresh air at each breath.

On comparing the heart with this behavior of the respiratory apparatus we find that the heart likewise varies its rate two- or threefold, from about 70 per minute up to 150 per minute or more; but, unlike respiration, its rate rises even with slight exertion, and increases progressively with each increase of muscular effort. How then does its amplitude of beat vary? According to the all or nothing law each beat is maximal under the conditions prevailing. But does the law apply to this matter, and what are the conditions?

TWO CONTRASTING THEORIES. Progress in regard to this problem will be most assisted if we first formulate the two extreme alternative conceptions of the heart's behavior, and show the underlying principles of the variations in the rate of circulation of the blood according to each conception. We may then compare these conceptions with the evidence which the literature affords. It must not be assumed, however, that one conception necessarily excludes the other, for up to a certain point the heart may behave according to one, and beyond that point according to the other, or in some intermediate manner; and during extreme muscular exertion yet another and more or less abnormal behavior may occur. The range of cardiac activity which we shall consider is that lying between bodily rest with an oxygen consumption of 300 cc. per minute or less, and a pulse of 70 or less, up to an exertion such as

can be sustained by a vigorous man for a considerable time and involving an oxygen consumption of about 2,000 cc. per minute and a pulse rate of about 150 per minute.

The first and commonly held conception of the circulation may be termed the theory of variable amplitude of heart beat. It is based on the assumption that the circulation rate—the volume of blood pumped into the aorta per minute—is proportional to the oxygen consumption of the whole body; the circulation would thus in general be analogous to respiration in its behavior. As the oxygen consumption of the body may increase 800 or 1000 per cent over the resting value, while the rate of heart beat increases only about 150 or 200 per cent, that is, 60 beats per minute during rest and 150 to 180 during intense exertion, it is evident that this conception necessarily involves the assumption that the amplitude of the heart beat, its systolic discharge or stroke volume, is variable. In this respect also the heart's behavior would be like that of breathing. The result of this condition would be that, alike at rest and during work, the average venous blood returning to the right heart and mixed in its chambers would contain a nearly unvarying amount of oxygen, and of course, therefore, an unvarying deficit below that in the arterial blood. With this uniform "oxygen utilization," the partial pressure of oxygen in the tissues would also be (presumably) unvarying and as high during work as during rest; an obvious advantage.

The second and alternative conception is that of a nearly uniform maximal heart beat. According to it, the heart action is essentially unlike the respiratory movements of the chest, and there is a varying relation, instead of direct proportionality, between the body's oxygen consumption, or energy expenditure, and the circulation rate. The result would be that during rest the mixed venous blood in the right heart would contain only a little less oxygen than that in the left; during heavy work, on the contrary, the amount of oxygen utilized out of unit volume of blood in its passage through the tissues would render the (average mixed) venous blood far lower in oxygen than the arterial. The partial pressure of oxygen in the tissues during work might be lowered correspondingly. (But see p. 180.)

In the first conception the reserve of the circulation, its factor of safety, is almost wholly in the heart itself, in its variations both of stroke volume and rapidity of beat. In the second conception, the heart contributes only its ability for variation of rate, but not of amplitude, to the factor of safety and to the flexibility of the adjustment of the circulation to the body's demands. The remainder of the margin of

safety, in respect to the utilization of oxygen from the blood by the tissues and especially the working muscles, amounting to about ten times the resting value, lies in the fact that the blood contains from three to five times as much hemoglobin as a healthy man utilizes for oxygen transportation during rest. Thus if the heart rate rises to threefold and the oxygen utilization to three and a third, we have ($3 \times 3.33 = 10$) a tenfold variation, even with a uniform stroke volume. The latter conception has thus two considerations to support its probability: one physiological, the other pathological. It explains easily why the corpuscles and hemoglobin are maintained at four times the amount for which there is use during rest; and it explains why an anemic person is easily out of breath even on slight exertion, which according to the first theory should not be the case.

For the sake of still greater sharpness of contrast, let us put these conceptions into figures and thus compare in detail the conditions involved. Suppose a man of strong physique (such as Douglas, the subject of the most valuable experiment in the recent paper of Douglas and Haldane, whose data are here rearranged and generalized) weighing 66 kilos, who consumes 250 cc. of oxygen at rest with a pulse of 60, and 2,000 cc. of oxygen per minute with a pulse rate of 150 when working on a bicycle ergometer. His oxygen pulse, a term introduced by Henderson and Prince (1914) to express the oxygen consumption divided by the pulse rate, or the amount of oxygen which the heart forwards to the tissues at each beat, is 4.16 cc. during rest and 13.3 during work. How would the circulation transport the greater amount of oxygen during work according to the two conceptions? Suppose that, in accord with the first conception, the blood during bodily rest loses 6 volumes per cent of oxygen on the average in passing through the tissues of the body, and that the same rate of oxygen utilization is maintained during work; in other words, that alike in work and rest the blood in the right heart contains 6 cc. less of oxygen per 100 cc. of blood than that in the left heart. Evidently then the rate of circulation, or total blood discharged into the aorta per minute, must vary in direct proportion to the oxygen consumption. The blood flow during bodily rest would therefore be 4166 cc. per minute, and that during work 33,333 cc. Each divided by the pulse rate gives the stroke volume of the left ventricle: 69.4 cc. of blood for rest and 222 cc. for work. These relations are shown in table 1 A.

On the other hand suppose that with the same data of oxygen consumption, pulse rate and oxygen pulse, we should find that the oxygen

utilization during rest is only 3.33 volumes per cent, while during work it is 10.7: a relation which would still leave 6 or 7 volumes per cent of oxygen unutilized in the venous blood, since the arterial blood contains about 18 cc. of oxygen per 100 cc. of blood. Then the circulation in rest would be 7,500 cc. of blood per minute and during work, 18,700 cc.; and alike during rest and work the stroke volume would be 125 cc. These relations are shown in table 1 B.

TABLE 1

Illustrating two contrasting conceptions of stroke volume and circulation rate

Subject, man, 66 kilos

THEORY	OXYGEN CONSUMPTION	PULSE RATE	OXYGEN PULSE	OXYGEN UTILIZATION	CIRCULATION RATE	SYSTOLIC DISCHARGE	CONDITION OF SUBJECT	POSTULATES
	cc. per minute	*per minute*	*cc. per beat*	*volumes per cent*	*cc. per minute*	*cc.*		
A	250	60	4.16	6	4,166	69	Rest	Variable amplitude of beat and stroke volume, with uniform relation of circulation rate to oxygen consumption
	2000	150	13.3	6	33,333	222	Work	
B	250	60	4.16	3.33	7,500	125	Rest	Uniform maximal beat with varying relation of circulation rate to oxygen consumption
	2000	150	13.3	10.7	18,700	125	Work	

The evidence regarding these alternative conceptions lies in a number of quite separate fields, which we shall now survey.

LIMITING ANATOMICAL CONDITIONS. It is highly probable that during health even the largest systolic contractions never entirely empty the ventricles. Both plethysmographic observations on the heart (the volume curve) and x-ray pictures support the older evidence (as reviewed by Tigerstedt, 1893 and 1907) that at the end of systole a considerable volume of blood remains in the ventricles; at least a quarter, perhaps a third, or even a half as much as the systole discharges into the arteries. The systolic size of the heart depends both on tonus and on the amplitude of contraction. The diastolic size depends upon tonus and amplitude of relaxation, amount of venous pressure and inflow, and finally upon the pericardial sack.

The heart is not free to expand indefinitely, for one need only inspect the heart of an animal killed quickly by asphyxia to see the chambers so distended that the pericardial sack is stretched tight. Barnard (with Leonard Hill) showed that the pericardium is practically inextensible, and that it can bear a pressure of $1\frac{1}{4}$ to $1\frac{3}{4}$ atmospheres. He found that the dead heart, in which tonus is completely absent, can expand to twice the size upon opening the pericardium that it can with the pericardium intact. Evans and Matsuoka found an increased gaseous exchange in the heart, indicating increased work, after opening the pericardium. Kuno (with Starling) found in the heart-lung preparation that opening the pericardium had a very distinct effect in increasing the amount of blood pumped by the heart when the venous inflow was large. In particular the pericardium seemed to protect the right heart from over distention. His opinion "that the pericardium exercises under every condition of venous inflow a certain amount of resistance to the diastolic expansion of the heart, which increases with any increase in the heart volume," seems however, very improbable. His opinion that "the existence of the pericardium is necessary for the unimpaired working of the heart in normal life" is negatived by the investigations of Yamada, who (working in association with Kuno later) found that animals, in which the pericardium had been cut open aseptically, the chest closed again, and the subjects restored to normal health, were able to make vigorous physical exertion with no injury to the heart. He offers the very probable explanation that during increased rapidity of beat, the corresponding increase of tonus prevents the ventricles from dilating so far.

It seems probable from these observations and from the volume curve (see below), that if the pericardium in a normal man or animal limits the extent of dilatation at all, this occurs only during a period of very slow beats and very low tonus during sleep: it is not protective against cardiac strain. All the ordinary volume changes of the heart probably fall short of either of the limits of diastolic distention and systolic contraction thus defined, and depend upon the behavior of the heart itself under the control of nervous, chemical and mechanical conditions, the latter chiefly venous pressure. It is, however, of some interest to know the possible maximal volume change in man between these limits.

To determine this point Henderson and Prince (1914) made the following observations: On six cadavers at autopsy, 3 men and 3 women, water was run into the pericardial sack, through a funnel, rubber tube

and hollow needle, up to maximal distention, and the amount was measured. The volumes of blood obtained from the heart's chambers later in the autopsy were also measured. The sum of the two measurements gave figures of 650, 700 and 620 cc. respectively in the men; and in the women, 633, 430 and 350 cc. As two of the men were young and of good muscular development, 700 cc. represents a fair estimate of the normal maximum volume. Bohr had previously made similar determinations on the pericardial sack of the horse and found 2 liters for each side of the heart in a horse of 500 kgm. He concluded that even if the heart passed from the greatest distention which the sack would allow down to complete emptiness at each stroke, the systolic discharges would be insufficient to allow an oxygen transportation equal to the maximum oxygen consumption of the animal during hard work found by Zuntz and Hagemann; Bohr (with Henriques) was thus trying to show a considerable consumption of oxygen in the lungs, a conception no longer supported by anyone. Zuntz (1911 and 1912) in answering Bohr and Pütter had the matter reinvestigated by Müller (1911), who found the total pericardial volume in the horse 0.78 to 0.93 liter per 100 kgm., virtually agreeing with Bohr's figures. Some observations on dogs and rats in this laboratory (unpublished) have yielded figures of the same order in cubic centimeters per kilo.

If we use the figure 700 cc. for the pericardial volume in man and assume that each auricle has half the capacity of its ventricle, we have 233 cc. as the extreme volume which the sack would allow each ventricle to expand and contract. According to the theory of variable systolic discharges, as shown in table 1 A, such a man as is there considered must have a stroke volume, if the first theory is correct, of 222 cc. when the amount of body exertion consumes only 2,000 cc. of oxygen per minute. As a vigorous man may do far more work than this and consume a much larger amount of oxygen per minute, the first theory in its strictest form would seem to require that for an oxygen consumption of 3,000 cc. per minute, the ventricles should be distended to the full amount that the pericardial sack would allow during diastole, and contract to the obliteration of the chambers during systole; and even then the heart would fall short of accomplishing its task. Hiffelsheim found, by filling the ventricles with wax, a capacity of only 156 cc. for the left ventricle of man, and the right slightly larger. Keller has made similar measurements.

To sum up, the pericardial volume for all the animals and men observed is about 3.5 to 5.0 cc. per kilo body weight for each side of the

heart. It will be shown below that the maximum stroke volume of each ventricle is probably about 1.5 to 2.0 cc. per kilo for all vigorous mammals.

EQUATIONS OF OXYGEN CONSUMPTION AND BLOOD CIRCULATION. In considering the investigations to be reviewed below, it is essential to keep particularly in mind the inverse relation of the stroke volume of the heart to the amount of oxygen (in volumes per cent) utilized from the blood. The oxygen pulse (the oxygen consumption divided by the pulse rate) is easily calculable for every heart rate and degree of muscular exertion in man. If then, for example, the oxygen pulse, S_o, is 6 cc., and the oxygen utilization, U_o, is 4 volumes per cent, the stroke volume, S, is necessarily 150 cc.; or stated in general terms, the solution of our problem by the respiratory or blood gas method (as shown hereafter) turns upon determining the oxygen utilization and then calculating the stroke volume by means of the expression:

$$S = \frac{S_o \times 100}{U_o}$$

Evidently if S is a constant for the individual, the relation of U_o to S_o is also constant.

This expression is a derivative of the equation generally used in this connection in which M is the minute volume or total circulation rate, O is the oxygen consumption of the body per minute, and U_o the oxygen utilization in volumes per cent, and which is as follows:

$$\frac{M}{O} = \frac{100}{U_o}$$

The oxygen pulse from such data as are now available appears to be nearly uniform (about 3.5 cc. to 5.0 cc. for a 60 or 70 kilo man) at rates below that of sitting rest (about 70 beats per minute), rises rapidly up to heart rates of 100 to 120 per minute (12 to 15 cc. oxygen per beat) and then less and less rapidly with further acceleration of the heart rate. There are probably marked differences between athletic and sedentary individuals, and considerable variations in the individual depending upon the momentary degree of nervous excitement, and upon whether large muscle masses are worked moderately or small masses vigorously with the same oxygen consumption.

To express our problem in its simple terms: The theory of a nearly uniform maximal heart beat, as large during rest as during work, is

tenable only if it can be shown that in vigorous normal men and animals the oxygen utilization during rest is quite small, 3 to 5 volumes per cent or less; but if this condition can be demonstrated this theory is thereby virtually established. On the other hand, the finding of a stroke volume of only 0.3 cc., or less, per kilo at a normal venous pressure, as in many experiments by means of the stromuhr and on the heart lung preparation, would necessitate the acceptance of the theory of a considerable oxygen consumption in the lungs: a point on which Tigerstedt (1905) has justified the correctness of Bohr's argument.

In spite of many opposing witnesses, evidence is accumulating that the condition of a very small oxygen utilization during rest is fulfilled in vigorous men.

Observations by respiratory methods. The classic work of this type is that of Zuntz and Hagemann on the metabolism of the horse during rest and work. In the chapter on the work of the heart in that animal, using the methods first suggested by Fick (1870 and 1886), they estimated the circulation rate from the following data: *a*, amount of oxygen absorbed, or CO_2 exhaled by the lungs; *b*, the amounts of oxygen and CO_2 in blood drawn from an artery; and *c*, the amounts of these gases in blood drawn from a sound inserted through the jugular vein into the right heart. The differences in respect to the oxygen and CO_2 in the arterial and mixed venous blood divided into the total oxygen or CO_2 of respiration per minute gave the circulation rate. As the average figures for the best nine or ten experiments on animals of the average weight of 347.6 kgm. at rest, they found differences between the arterial and venous blood of 7.44 volumes per cent oxygen and 7.16 volumes per cent CO_2; and for work differences of 9.34 for oxygen and 8.17 for CO_2. Arterial blood in the rather poor horses used contained 14 or 15 volumes per cent of oxygen, but in vigorous animals was estimated by Zuntz to contain 19.5. As the oxygen consumptions were 2080 cc. at rest and 5007 cc. during work, the blood pumped out of the left heart per minute figured out to 29,155 cc. during rest and 53,034 cc. during work. No counts of the pulse rate are given in their protocols, but the rates assumed were 40 beats per minute in rest and 55 during work. The stroke volumes calculate to 729 cc. during rest and 964 cc. during work, or 2.09 cc. per kilo body weight for rest, and 2.77 cc. per kilo for work. (If 70 beats per minute were assumed during work, the systolic discharge would have been the same as during rest.) The attention of the investigators was fixed, not primarily upon the blood flow, but upon the work of the heart (the circulation rate multi-

plied by the arterial pressure), and for this purpose the actual pulse rates were unimportant.

The lack of precise counts of the pulse deprives this work to a considerable extent of the evidential value sometimes assigned to it in favor of the theory, which Zuntz always defended,[1] of a variable amplitude of heart beat, increasing during physical work. The stroke volume determined during rest (2.09 cc. per kilo) is, however, not subject to this criticism. In one experiment of intense work, in which the animal consumed 22,942 cc. of oxygen per minute, Zuntz and Hagemann estimated that 245.5 liters of blood were pumped in 70 beats of the heart, or 3.5 liters per beat by each ventricle, or about 10 cc. per beat per kilo body weight. Here surely there must be some gross error either in the original data or in the method of calculation. Bohr made very effective use of this experiment by pointing out that a stroke volume of 3.5 liters in a horse was an anatomical impossibility, and that the data were comprehensible only on the basis of a large consumption of oxygen in the lungs: a contention which Zuntz rejected, but which on account of this experiment he had some difficulty in explaining away. Bohr held it to be extremely improbable that the heart is capable of doubling its rate of beat and its stroke volume simultaneously.

While inclining in the main toward the theory of variable heart beat, Zuntz and Hagemann nevertheless say expressly that "in the working animal the circulating blood is better utilized than during rest, in that per unit blood more oxygen is withdrawn and more CO_2 added in the tissues."

Grehant and Quinquaud had already carried out similar experiments on dogs, but based their conclusions on determinations of the excess of CO_2 in the venous blood over that in the arterial blood, amounting in six experiments to 11.3, 8.5, 4.6, 4.0, 4.2, 5.5 volumes per cent of CO_2. They report no experiments during muscular activity and no counts of the pulse; but merely give the calculated circulation rates, varying from 512 to 2614 cc. for dogs from 7 to 18 kilos. If we assume that the smaller figures are for the smaller dogs and the larger for the larger dogs, and further that the pulse was always 100, we find stroke volumes of 0.73 and 1.45 cc. per kilo respectively.

[1] At the International Physiological Congress in 1910, the reviewer presented evidence for a uniform stroke volume from volume curves, and had the honor of a brief debate with Professor Zuntz over this matter,—a debate greatly hampered by linguistic difficulties—in which Professor Zuntz strongly objected to the view presented.

Loewy and von Schrötter attempted the solution of this problem on man. Following the lead of Pflüger and his pupils, Wolffberg and Nussbaum, in the use of a similar technique on animals they inserted a catheter or sound through the mouth and trachea in such a way as to close off the right bronchus or one of its larger branches. Air samples could be drawn at intervals from the part of the lung thus cut off from external ventilation, and it was found that the gases which it contained quickly assumed a uniform composition, corresponding to the tensions of the gases in the venous blood coming to the lungs. By applying the oxygen tension thus found to the oxygen dissociation curve of blood, a value for the oxygen content of the venous blood was obtained. A corresponding value for the arterial blood was obtained from the percentage of hemoglobin in the blood and the oxygen in the air in the ventilated lung, so that the oxygen utilization was calculable. It was found that the CO_2 tension of the venous blood was surprisingly low, only 6 per cent of an atmosphere. The oxygen utilization during rest was 6.5 cc. per 100 of blood. For a 60 kilo man therefore, during rest, the circulation rate was figured at 3.85 liters per minute. They concluded that the stroke volume is subject to wide variations, but is on the average 55 cc. for a 66 kilo man, or 0.83 cc. per kilo body weight.

Although Loewy and v. Schrötter discuss the effect of work upon the circulation, their experiments on this topic were few and the amount of work so small, as judged by the oxygen consumption, as really to throw little light on the subject.

Plesch, working in part in Zuntz's laboratory, greatly simplified the technique of estimating the venous blood gases in man from respiratory data. His procedure in principle consisted in breathing back and forth for 15 to 25 seconds into a small rubber bag so that the air in the bag came to be of the same composition as that in the lungs and was thus in gaseous equilibrium with the venous blood. The CO_2 tension was thus easily determined. To obtain the oxygen tension it was necessary that the bag at the outset should be filled with nitrogen. In this way without risk or inconvenience to the subject, the gas tensions of the venous blood were obtained and the oxygen content calculated. Although Plesch does not emphasize the point, his data show that the CO_2 partial pressure of the venous blood is, as Loewy and v. Schrötter had also found, only a little above that of the arterial blood. The oxygen utilization in 5 normal people at rest was 7.4, 4.3, 7.15, 5.74 and 4.26 cc. per 100 cc. of blood. In a healthy resting man of 68 kilos, he estimates the minute volume of the circulation at 4,300 cc. and the

stroke volume at 59 cc. or 0.86 cc. per kilo body weight. He holds that the circulation rate depends upon the combustion in the tissues, but that the increase is not proportional to increase of oxygen consumption during work. He considers that the blood never loses more than two-fifths of its oxygen in passing through the tissues. He estimates the highest possible minute volume during the most violent work at 47 liters of blood and the stroke volume, in a man working hard, at 240 cc. But he did no experiments and made no measurements during work.

Bornstein also attempted to estimate the volume of the blood stream in man from respiratory data. The lungs were rapidly washed out with oxygen and the subject thereupon breathed through a potash cartilage into a bag filled with oxygen. From the rate at which the nitrogen dissolved in the blood was given off to this atmosphere of oxygen, he calculated the volume of blood passing through the lungs. His data figure out to a minute volume of 6 liters for rest, but during work would indicate, as Krogh justly comments, the impossible minute volume of 60 liters.

Markoff, Müller and Zuntz utilized the breathing of nitrous oxide for the purpose of estimating the circulation rate in man. In one determination they found the stroke volume of the heart 96.7 cc., which they regarded as too large. In another determination on the same subject they found 43.9 cc.

Krogh and Lindhard (1912) developed the nitrous oxide method independently. In their procedure the gas (10 to 25 per cent nitrous oxide in air enriched with oxygen) is held in the lungs for a period of less than the time of a full circulation. At the beginning and end of this period, which must be accurately measured, an alveolar air sample is obtained and analyzed particularly for nitrous oxide and for oxygen. The total volume of gas in the lungs is also estimated from previous respiratory data, the oxygen consumption of the body is determined either before or after the nitrous oxide experiment, and the pulse is counted. From these data and the coefficient of distribution of nitrous oxide between the air and blood in the lungs, the blood flow per minute through the lungs is calculated. There are thus a number of factors to be estimated and combined, and the observational errors in alveolar air methods, as Krogh and Lindhard (1914 and 1917) have themselves pointed out in a critique of the work of some other investigators, may be considerable. It is to be expected, therefore, that in the combination of the various factors during a calculation, the observational errors may

in some cases neutralize one another, and in others may be summated in the results. When we examine these results, we find exactly the sort of variations to be expected on these grounds. The investigators themselves seem, however, to assume that the widely varying systolic discharges and circulation rates, which they obtain even in the same subject under identical conditions on different days, are correct expressions of physiological variations in heart action, instead of mere experimental errors and variations. Particularly in a later paper (in Pflüger's Archiv, clxi) in which Lindhard (1915) reports numerous observations, the variations between successive determinations are very large. Thus for example in table XIc, the subject J. J. on February 22nd, during work involving the consumption of 870 cc. of oxygen and a pulse rate of 92, showed a stroke volume of 160 cc., and 4 days later with the same pulse rate and the same oxygen consumption, the stroke volume was only 88 cc. Again in table IX, the subject J. L. on June 19th with an oxygen consumption of 225 cc. and a pulse of 64 showed a stroke volume of 71 cc., but on November 26th, with an oxygen consumption practically the same and the same pulse rate, the stroke volume found was only 49 cc. These are extreme examples, but to a considerable degree variations of this type run through all the data reported by Lindhard.

Such variations would not, however, necessarily invalidate the conclusions, for Lindhard (1916) has obtained so large a mass of observational material that he is able to treat it statistically. Statistical treatment does not, however, eliminate a fundamental disturbing element; and such an element in this work lies in a correction which is applied to all of the blood flow measurements. This correction depends upon the fact that during the experiment itself, while nitrous oxide is being held in the lungs, the oxygen consumption apparently differs markedly from that during the fore and after period; the difference amounting in some cases to an increased rate of absorption of 60, 80 or even 100 per cent or more. The figures finally calculated for blood flow and stroke volume are therefore corrected, that is, reduced, by corresponding amounts. The extent of the correction in some cases may be illustrated (from table V) by the subject J. J. on whom between the 8th and 15th of October were obtained the following figures for the minute volume of the circulation (in liters). The unreduced figures as calculated directly from the observations are here placed above the "corrected" figures:

Observed	8.8	10.3	9.5	9.7	7.7	7.9	9.0	7.0
Corrected	7.4	8.55	7.9	6.5	5.6	5.7	4.2	3.0

Some of these, notably the last two, are indeed enormous corrections and render the "corrected" figures much more variable than those directly obtained, which latter are, it now appears, also probably much nearer the true values.

This correction is in many cases inconsiderable during experiments on work, and Lindhard's measurements of the minute volume of the circulation and the systolic discharge during work are, on the average, aside from the experimental variations, probably of the correct order of magnitude. The determinations during rest, in the light of later work to be reviewed below, are probably only 50 to 60 per cent of the correct value. It is true that the correction itself appears at first sight logical; but it requires us to assume that nitrous oxide exerts no pharmacological effect, and also to believe that during the holding of the breath after 3 full breaths the circulation may be accelerated even up to 100 per cent. In fact, however, little is known of the pharmacological action of nitrous oxide; and the radial and carotid pulse give to one's finger no indication of such augmented beats during such breathing and pause; as the reader may immediately convince himself. It may be mentioned also that in connection with the Pike's Peak expedition (Douglas, Haldane, Henderson and Schneider, prior to the publication of the work of Markoff, Müller and Zuntz and that of Krogh and Lindhard) the reviewer had independently attempted to utilize nitrous oxide to determine the circulation rate. In these experiments it was found that marked functional disturbances of an obscure character in respect to the absorption of oxygen occurred and that the results obtained were subjected to so much doubt and error that the method was not developed.

Douglas and Haldane have justly pointed out that one of the probable sources of error in Krogh and Lindhard's method lies in the first alveolar sample giving an oxygen percentage higher than existed at the moment in the deep alveolar air. Lindhard (1922) in his latest paper seems to concede at least in part the validity of the objection.

The general conclusions reached by Krogh and Lindhard and by Lindhard in later work are that "the blood flow during rest varies between very wide limits (from 2.8 to 8.7 liters per minute) depending upon the variable supply of venous blood to the right heart." When a series of consecutive determinations is made "a remarkable constancy is, however, generally observed." (But compare the figures above quoted.) "During muscular work the rapidity of the circulation is greatly increased, the maximum observed being 21.6 liters per minute.

Oxygen utilization during rest is expressible by coefficients varying between 0.28 and 0.60 rising to 0.73 during muscular work." "The stroke volume may fall as low as 26 cc. during rest." Lindhard concludes that "during rest the minute volume is a function of the respiratory metabolism, a metabolism of 200 cc. of oxygen corresponding to a blood flow of 3.5 to 4 liters." The coefficient of utilization of oxygen from the blood is 0.3, a little higher for women and a little lower for men. The systolic discharge of the heart is in all cases a secondary function determined by the two independent variables, minute volume and pulse frequency. During muscular work the minute volume may increase sixfold while the metabolism increases tenfold, and the oxygen utilization may then reach a coefficient of 0.795, corresponding to 14.85 cc. of oxygen per 100 cc. of blood.

In spite of the technical defects of the nitrous oxide method, it is probable that the average of the observations for the circulation rate and stroke volume during muscular work is of the correct order of magnitude. It may be pointed out also that if Krogh and Lindhard had not felt compelled to reduce their values by the correction above mentioned, the average of their determinations on rest would also be in accord with later and more accurate estimates of the circulation rate and stroke volume for this condition. Indeed it is noteworthy that in some experiments they found a figure (103 cc.) for the stroke volume during rest which as they point out "falls very little short of the largest stroke (116 cc. recorded, or 127 cc. assumed) during work."

The nitrous oxide method has been used also by Fridericia (1916, 1918), Liljestrand, Boothby, and Means and Newburgh, with results generally similar to those above quoted. They find stroke volumes of 1.5 to 2.0 cc. per kilo body weight during work, but only about half or two-thirds as large during rest, and subject to wide variations under identical conditions.

Means and Newburgh have also attempted to calculate the circulation rate and stroke volume from the oxygen unsaturation of blood drawn from a vein in the arm. Assuming the arterial blood to be 95 per cent saturated, the coefficient of oxygen utilization was thus found in one observation 0.29 and in another 0.49, or about 6 and 9 volumes per cent. From these data the stroke volumes would figure to 75 and 34 cc. Similar figures could be based on analyses of the arterial blood and blood from an arm vein of normal men contained in papers by other recent investigators. Thus Lundsgaard's (1919) data show an oxygen utilization of 5.5 volumes per cent; those of Stadie 4.9 to 6.3;

and those of Harrop 2.5 to 8.3. In dogs Doisy and Beckmann report finding differences in the oxygen content of blood in the femoral artery and vein varying in 17 subjects from 2.1 to 18.1, average 6.1 volumes per cent. Uyeno and Doi find similar variations in the cat. Lundsgaard and Möller find that after vigorous exercise (stair climbing) the oxygen content of the blood from a vein in a man's arm is much decreased.

Unfortunately the oxygen utilization in a vein draining merely muscles and skin can afford no reliable indication of the oxygen utilization for the whole blood stream. Leonard Hill and Nabarro have shown that the coefficient of oxygen utilization for blood passing through muscles is 0.7 or 0.8, which would be 12.5 to 14.5 volumes per cent for human blood, while that for blood from the brain is only 0.2 or 0.3. Barcroft (1920) also notes the striking contrast between the color of the bright blood from the kidneys and the dark color of that returning from the hind legs as seen in the rabbit at the junction of the renal veins and the vena cava. In view of such observations as these, it seems quite possible, although paradoxical, that although the oxygen utilization for the whole blood stream is very much higher during muscular work than during rest, each tissue or organ has a nearly unaltered percentage utilization. It is the greater quantity of blood flowing through the muscles during work (Chauveau and Kaufmann) which causes the higher utilization for the whole blood stream. During progressive asphyxia practically the whole oxygen load of the blood may be utilized (Greene and Greene).

Boothby, Fridericia, and Liljestrand and Lindhard have also used the Fick principle for determining the blood flow in man, with results similar to those from the nitrous oxide method.

The most important advance in this field in recent years has come from the work of Christiansen, Douglas and Haldane. They demonstrated the mutual interaction of oxygen and CO_2 in the blood and were the first to work out the dissociation curve of CO_2 in blood: technical matters which are fundamental for valid work in application of the Fick principle to man. They also began the work on the measurement of the blood flow which has now been completed by Douglas and Haldane (1922). These investigators show for the first time on man that, at least in vigorous subjects, the stroke volume of the heart may be a quantity nearly uniform in work and rest. They say "In Douglas the circulation rate was nearly in proportion to the pulse rate. This corresponds to the conclusion reached in 1906 by Yandell Henderson from plethysmograph records of the heart beats in dogs. It has been inferred that Henderson's conclusions must have been mistaken, since

assuming as has hitherto been done that the mixed venous blood loses at least a third of its oxygen during rest, an increase to ten times or more in the metabolism during work could not possibly be brought about without a very large increase in the output per beat. The figures for Douglas show, however, that no increased output per beat, but only the actual increase of about three times in the pulse rate was needed for an increase in metabolism to ten times the basal rate. In none of our subjects was the circulation rate during work increased in even approximately direct proportion to the increase in metabolism, until the metabolism had been greatly raised."

The essential feature of these observations is that in such a subject as Douglas (66 kilos) the stroke volume (125 cc., or 1.9 cc. per kilo body weight) and the circulation rate (7,500 cc.) are so large that during rest the coefficient of oxygen utilization is only about 20 per cent, or a difference of only 3.2 volumes per cent in the oxygen content of the blood in the two sides of the heart. Thus when work is done the increased pulse rate (up to threefold) and the increased oxygen utilization from the blood (up to three- or fourfold) together provide for a tenfold augmentation of the energy expenditure and respiratory metabolism. (See table 1, page 169.)

On the whole it seems probable that a low coefficient of oxygen utilization during rest and a stroke volume as large during rest as during work are characteristics of vigorous athletic men. A stroke volume of 1.8 to 2 cc. per kilo body weight during work is quite in harmony with other investigators, but it is twice as large as has generally been believed heretofore to occur during rest. The idea involved may be illustrated by comparing the conditions in so unenergetic an animal as the domesticated goat, with the conditions in dogs. Thus Barcroft and his collaborators (1920) have found that in the goat with 66 per cent hemoglobin (Haldane's scale) the difference in the oxygen content on the two sides of the heart is 4 to 7 cc. of oxygen per 100 of blood. The minute volume per kilo works out to 133 cc.

On the other hand in experiments (as yet unpublished) of a similar character, performed in this laboratory by Haggard and the writer upon dogs, the blood in the left heart contained 20 volumes per cent of oxygen and 39 of CO_2, while that in the right heart contained 17 oxygen and 41 CO_2: difference, 3 volumes per cent oxygen, and 2 CO_2. This low coefficient of utilization indicates a stroke volume of 1.9 cc. per kilo body weight; the heart rate was 130 per minute. In another experiment the arterial gases were 16.5 oxygen, 47.5 CO_2, while the venous

gases were oxygen 12, CO_2 51; difference 4.5 oxygen and 3.5 CO_2. The stroke volume figures therefore to 1.58 cc. per kilo body weight at a pulse rate of 126 per minute. In a third dog the difference between the blood gases in the right and left hearts was 3.5 oxygen and 1.5 CO_2. Evidently goats have only a small reserve in respect to oxygen utilization upon which they can draw during exertion, while dogs have an enormous reserve, 400 or 500 per cent. The capacity for vigorous exertion would thus be 2 or 3 times as large in dogs as in goats.

That vigorous men are in this respect comparable to dogs rather than to goats in the smallness of the difference in the amount of CO_2 in arterial and venous blood during rest has been found by Henderson and Prince (1917) in a number of determinations (still in progress, Henderson, 1922) by a development of the respiratory method. The CO_2 tension in the alveolar air or (as it were better termed) "arterial pulmonary air" is determined by Haldane's method, while that in the "venous pulmonary air" is found by rebreathing, by Plesch's method air containing about 6 per cent CO_2 and a high enough oxygen content to nearly saturate the blood with this gas. This gives, not the true venous CO_2 tension, but that for venous blood which has been saturated with oxygen without loss of CO_2. Both the arterial and the virtual venous CO_2 tensions thus obtained may then be applied to the CO_2 dissociation curve of fully oxygenated blood (a curve of which the slope is sufficiently uniform, although the absolute level varies individually) to obtain the corresponding figures for the CO_2 contents of the arterial and mixed venous bloods. The CO_2 difference (in volumes per cent) multiplied by the inverted respiratory quotient gives the oxygen utilization.

In healthy men at rest the values thus found are seldom more than 3 or 4 volumes per cent of CO_2 difference in the arterial and venous bloods; and although larger differences are sometimes found, they are generally observational errors rather than true indications of slower circulation. Barcroft, Roughton and Shoji report that the method of Henderson and Prince gives results in close agreement with a more refined method of the same general character employed by them. The CO_2 differences found by Barcroft and his co-workers on two subjects were 4.0 and 3.3 cc. Redfield, Bock and Meakins also confirm the method of Henderson and Prince and report correspondingly low CO_2 pressures in the venous blood.

Meakins and Davies (1922) by a method essentially similar to those just mentioned have obtained very concordant and significant results.

On four human subjects they find the stroke volume to be during rest 100, 150, 132 and 96 cc. and on a fifth subject 121 cc. during rest with an oxygen consumption of 217 cc. per minute, and practically the same stroke volume, 122 cc., during exercise on a bicycle and with an oxygen consumption of 1104 cc.

We know that man is a very vigorous animal. It appears from these data that his vigor in great part is based upon the large factor of safety afforded by a low oxygen utilization, with a correspondingly large stroke volume, during rest.

OBSERVATIONS ON THE CIRCULATION TIME. Numerous attempts have been made to estimate the heart action in man from observations on the peripheral circulation. Such methods as the arm plethysmograph (Fick, 1869; Hewlett, 1909), the hand calorimeter (Stewart, 1911), and similar procedures have yielded valuable evidence in their own fields; but they have not contributed materially to knowledge of the stroke volume of the heart and the velocity of the total blood stream.

The attempt to develop a rule by which the product of the pulse rate multiplied by the pulse pressure would serve as an index of the circulation rate in man has given a method of some value for purposes of comparison, but has not thrown much light on absolute quantities. (Dawson, Erlanger and Hooker, Skelton). Nor has it yet proved practicable, except for comparisons, to utilize as an estimate of the heart's activity, the recoil curve of the whole body (Henderson, 1905, Heald and Tucker). This curve records a movement of the body of about 0.1 mm. headward and feetward under the influence of the mass movements of the heart and blood, when the subject lies on a table in delicate suspension. Very little evidence of value on our topic has come from sphygmographic or electrocardiographic methods.

The duration of a circulation, the time required for the blood to complete the round and return to the same point, was first determined by E. Hering. He showed that in mammals of different sizes the circulation rate varies as the body surface. If the total volume of blood in the body is known, and if the velocity at all points and in all organs were equal, this method would be effective. Hering injected an easily recognizable non-poisonous substance, potassium ferrocyanide, into a vein toward the heart, and noted the time until the substance appeared in the blood flowing from another similar vein. The method was also utilized by Volkmann, who found on several species of animals that the stroke volume of the heart was 2.5 cc. per kilo body weight.

By Vierordt the method was refined and yielded much valuable information. He found that in mammals of widely different sizes, goat, dog, man and horse, the circulation time was in all cases between 26 and 28 heart beats. (In determinations of the venous pulmonary air by the Plesch method in this laboratory the second rise of CO_2, indicating completion of the shortest way round the circulation, is found to occur in approximately this number of heart beats in man.) This is a striking example of relativity, as the pulse rate in the rabbit is 4 or 5 times as rapid as in the horse, while in animals of intermediate weight the pulse rates correspond with the relative size. For mammals of all sizes, according to Vierordt's results, the stroke volume has the same magnitude in cubic centimeters per kilo body weight; and the circulation rates in mammals of all sizes, in cubic centimeters per minute per kilo body weight, vary therefore as the pulse rates. Vierordt figured the stroke volume at 2.83 cc. per kilo. v. Kries pointed out, however, that as the blood passes through some organs more rapidly than through others, as evidenced by its varying venosity, the stroke volume thus calculated would be too high and the indicated circulation rate too rapid.

Vierordt's conceptions appear to the reviewer much nearer probable truth than those of most later investigators, and combined with other data in this review they suggest the probability of the following laws (modified from Vierordt's statement): *1.* The average duration of a circulation through the shortest channels in all vigorous species of mammals at rest is equal to the average time of 27 $\pm$ 3 heart beats of the species. *2.* In different species of vigorous mammals there is direct proportionality between the blood flow (expressed in cubic centimeters per kilo per minute) the resting pulse rate, the oxygen consumption per kilo, and the surface: weight ratio; all four values for different species are thus proportional to each other. *3.* The stroke volumes of the hearts in species of mammals of different sizes vary directly as the body weights for all species of active mammals. In physiology such laws are never better than rough approximations and this formulation is offered not as definitely proved, but as valuable for test and suggestion. The more one studies the literature upon which this review is based, and data which lack of space prevents reproducing here, the stronger becomes belief in the essential correctness of some formulation of the sort here amplified on Vierordt's foundation.

The method of the circulation rate has been used from time to time by later investigators and notably in a modified and improved form by

Stewart (1894, 1921), who injected 1.5 per cent NaCl solution into a vein and determined its appearance in an artery by the change in electrical conductivity of the blood. In a typical experiment 33.5 cc. of salt solution were injected in 12 seconds. When the telephone indicated the arrival of the diluted blood in a branch of the femoral artery, 25 cc. were drawn during the 7th to the 17th second. From this sample the extent to which the blood was diluted was determined and the amount of blood discharged by the left heart was calculated. By this method in dogs values for the stroke volume of from 1.7 cc. in large animals to 3.2 cc. in small animals were found. Stewart, however, concluded that the circulation rate can vary considerably even at a constant pulse rate or may remain the same during a varying pulse rate. He argued that the stroke volume would grow smaller per kilo body weight as the size of the body increased and he therefore estimated the stroke volume of man at about 75 cc.

DIRECT MEASUREMENT OF BLOOD FLOW IN OPERATED ANIMALS. There have been many attempts to determine the stroke volume and circulation rate by measurements of the blood flow particularly in dogs and rabbits by such techniques as the stromuhr (R. Tigerstedt, 1891; C. Tigerstedt, Elving and v. Wendt), the plethysmograph for the whole heart (Roy and Adami, Johansson and Tigerstedt), and other related devices. The results present an almost complete disagreement from those views toward which the preceding sections have led us. They are not concordant among themselves, except in the smallness of the circulation rates and stroke volumes which they indicate. They are so far from grouping themselves under any definable principle, that one might infer from them that the heart may normally make nearly any size of stroke, large or small, at any rate of beat.

The size of the stroke volume was one of the problems which interested Ludwig, and evidence bearing on it appears in many of the classic papers of his pupils such as Pawlow, Dogiel, Bohr, Stolnikow and others. (See Tigerstedt's review, 1905.) Stolnikow in particular used a simplified circulation in which, after tying off all the arteries except the axillary, he caught and measured the blood flowing from this one vessel, and then returned it to a vein. The results obtained indicated a stroke volume of from 0.32 to 1.6 cc. per kilo body weight, with a general value less than 0.64 cc. Zuntz states that the work of Ludwig and his pupils indicates a capacity in the heart to vary its stroke tenfold, and actual variations of threefold under nearly uniform conditions.

Dogiel attempted to use a stromuhr in the aorta, but with commendable and rare frankness declared his results valueless on the point which is here of interest. R. Tigerstedt (1891) later employed the same method and also expressed doubt of the significance of the results, which showed values of 0.27 cc. per kilo body weight on the average of what he regarded as the best experiments, and 0.42 cc. for the average of all. As Tigerstedt (1905) points out, the smaller value would afford a blood flow of such insufficient amount as to drive one to the hypothesis, which Bohr and Henriques supported, but which is now no longer supported by any investigator (since Pütter, 1911), that the normal blood flow is not sufficient to supply to the tissues as much oxygen as the body actually consumes, and that therefore a considerable combustion must take place in the lungs.

In his review in the Ergebnisse der Physiologie, R. Tigerstedt (1905) quotes extensively the work on the circulation rate in the rabbit, as measured by a stromuhr inserted in the aorta, carried out by Carl Tigerstedt. This work was certainly of the highest quality as regards technical skill and care; and yet it would be difficult to find more widely varying measurements of any function than are there reported. The general impression, which this and similar work by many other investigators in this field makes upon one who turns to it for information, is that the rate of heart beat has so little relation to the circulation rate, and that the stroke volume therefore is so variable that any precise formulation of relations is excluded.

In considering the results obtained in this field by Ludwig's pupils and their successors, we must keep in mind that the animal under experiment is usually immobilized, morphinized, anesthetized, partly bled, cold, over-ventilated, and in general more or less advanced in that depression of vitality which (as we now know) is most significantly indicated by a decreased venous pressure. Decreased venous pressure indicates decreased venous return to the right heart, and induces in consequence a subnormal and varying diastolic filling and stroke volume of the heart.

Even under such abnormal conditions evidence of value may be obtained on points connected with arterial pressure, the vasomotor nervous control and the relation of the heart action to arterial pressure. But in their bearing on the circulation rate and the stroke volume of a normal man or animal in healthy rest or muscular activity, the great mass of observations in the literature of this branch of our subject is essentially misleading, for the observations insidiously substitute the data of depression, subnormal venous pressure and the first stage of shock for the data of health. Arterial pressure affords no reliable indication as to whether the circulation rate is of normal or somewhat subnormal value; only when the venous return and circulation rate fall beyond a certain point is

arterial pressure necessarily affected. Furthermore, in many of these investigations the distinction has not been sufficiently drawn between increased circulation rate effected by certain procedures, such as compression of the abdomen, or peripheral nerve stimulation, or infusion of adrenalin, as a momentary effect and as a continuous factor; for these procedures will raise venous pressure momentarily, but if continued do not maintain it; while only transfusion and hypercapnia appear to be able to achieve this effect in a manner at all imitating the high venous pressure (10 to 20 cm. of water) of muscular activity in normal life.

There is, however, a criterion for judging when there is and when there is not an adequate venous supply. Lying on his back a normal man exhibits a pulsation at the base of the neck which is almost wholly venous. The jugulars are distended. But when he sits up, or stands, the neck veins are usually collapsed and do not pulsate above the upper line of the clavicle: normal venous pressure does not rise so high (v. Recklinghausen). Similarly in an animal at the beginning of an experiment the jugulars when first exposed are usually seen to be full and pulsating; but as a surgical operation on man or an experiment on an animal progresses, the fulness and pressure in the veins decrease and leave then collapsed.

The filling of the right ventricle, and thus in consequence the stroke volume of the left ventricle, decrease correspondingly and progressively. It is not, however, the absolute venous pressure which is here concerned, but the "effective venous pressure" which is the difference, as Henderson and Barringer showed, between intrapleural pressure and the pressure in the great veins at the heart level. It amounts in dogs to 50 to 70 mm. water, but is probably somewhat more in man. This effective venous pressure is the force which distends the right heart in diastole, and subject to the diastolic receptive relaxation of the heart itself, determines the size of the stroke volume, and thus the fulness of the pulse, but not arterial pressure.

It is the general neglect of the venous return and pressure which explains why experiments on the blood flow in animals under operative conditions have afforded such extraordinarily, variable, discordant and abnormally low values. If less blood is coming to the heart per minute than the heart can pump even at a slow rate of beat, it is evident that the heart rate may be accelerated to any extent without changing the minute volume. On the other hand, if the heart rate remains the same, and some procedure is effected so that a venous return, which was at first very low and inadequate, is restored more nearly to an adequate volume, the circulation rate may vary widely even while the heart rate remains the same. This affords the explanation for the irregular observations on the circulation rate under operative and experimental conditions of which the literature is full. A normal venous pressure is a necessary condition for a normal circulation rate.

Probably 90 per cent of all the blood pressure and blood flow experiments in the literature of physiology were performed on animals in the first stage of shock; just as in nearly all patients who are under etherization and operation for more than one hour the superficial veins nearly or quite disappear, the skin is pallid (cutaneous capillary depletion) and arterial pressure tends downward.

The depressant action even of anesthesia without operation is shown by recent (unpublished) observations of Haggard in this laboratory; for in two dogs under morphine and ether in good condition prior to operation, the stroke volumes were found to be only 0.83 cc. and 0.78 cc. per kilo body weight. Analyses of the

ether content in the inspired and expired air and in the arterial and venous blood furnished the data for these calculations. Similarly Doi (with Barcroft) found the oxygen utilization to be 5.5 volumes per cent and the stroke volume of the heart only 0.74 cc. per kilo in a cat under urethane (see also p. 180).

Observations on the heart-lung preparation. The heart-lung preparation, or reduced circulation, was first utilized by Newell Martin and was adapted for investigation of our problem by his pupils, Howell and Donaldson. A cannula is tied into the aorta close to the semilunar valve, and is connected to a rubber tube leading to an elevated reservoir, in which the blood may be collected and measured. A similar arrangement, connected to a cannula tied into the superior vena cava, supplies defibrinated blood to the right heart under any desired head of pressure. All other systemic arteries and veins are tied off so that the blood circulates only through the heart and lungs, which are ventilated artificially, and through the rubber tubes and glass vessels. Howell and Donaldson found, as have all other investigators, that the stroke volume is scarcely at all affected by variations of arterial pressure; the heart discharges as large a volume against a high as against a low pressure. On the other hand, the stroke volume was found to be absolutely dependent upon the pressure at which the blood was supplied to the right heart. Howell and Donaldson estimated the stroke volume of the heart for dogs at 1.17 cc. per kilo body weight at 180 heart beats per minute; but in their experiments this volume was not reached in most cases until abnormally high venous pressures were applied. At normal venous pressure (5 to 7 cm. of water) the stroke volumes were only 0.5 cc. per kilo or less. This relation of venous pressure and stroke volume may be illustrated from one of their experiments, in which the heart of a dog of 8.6 kilos at rates of beat of 91±4 per minute behaved as follows (with the stroke volume in cc. per kilo calculated by the reviewer):

Venous pressure, cm.	10	20	30	40	50	60	65	70	10
Stroke volume, cc.	2.51	5.08	6.42	8.39	9.4	10.97	10.8	10.8	2.38
Stroke volume, cc. per kilo	0.29	0.59	0.74	0.97	1.09	1.27	1.25	1.25	0.27

The largest stroke volume, at 60 cm., was thus only 1.27 cc. per kilo, while that at 10 cm. a figure already above the normal effective venous pressure was less than 0.3 cc. per kilo. Edema of the lungs (due we may guess to the high venous pressure found necessary to overcome the abnormal undistensibility of the heart) brought many of the experiments to a speedy end.

The importance of the phenomena of muscular relaxation, particularly in relation to the total amount of work possible in a given time, has only recently begun to receive recognition. It is a priori probable that the speed of a runner over any short distance is dependent upon the velocity with which his muscles relax, and allow themselves to be stretched, quite as much as upon the velocity of their contraction. In similar fashion in the heart, the velocity and extent of relaxation, in other words, the ease with which the muscle stretches under the distending force of venous pressure, is probably quite as important a factor in the heart's behavior as the force and rapidity of the systolic contraction. Cannon (1911) has emphasized somewhat the same behavior in the stomach which he terms its "receptive relaxation." In the heart, as in the stomach, the diastolic receptive relaxation is a vital factor and not merely a mechanical stretching like that of a rubber bag. Being vital, it is variable. In the experiment above quoted the data of venous pressure and stroke volume show the heart to have been so abnormally resistant to distention that we must regard its behavior as outside the field of normal physiology and as belonging to an artificial pathology. As the blood employed in the experiments of Howell and Donaldson was necessarily excessively aerated, and its content of CO_2 and the ratio of H_2CO_3: $NaHCO_3$ were thus abnormally reduced, the behavior of the heart is explicable as the now well demonstrated result of such alteration in the blood.

Evidence obtained by a similar technique by Starling and his pupils in a large number of papers has led Starling to formulate what he terms the "law of the heart." It is an extension of the all or nothing law and defines the conditions determining the force of contraction; it were better called, therefore, the law of systole. In its strictest formulation Starling in his Linacre lecture defines it thus: Within physiological limits the larger the stroke volume of the heart, the greater are the energy of its contractions and the amount of chemical change at each contraction. In other words, the energy of contraction however measured is dependent upon the length of the muscle fibers. Any increase in the extent of active surface increases the energy of change, exactly as in striated muscle. Thus the uniformity of stroke volume against varying arterial pressures, which all investigators have found, depends upon the fact that, while the first few heart beats after a rise of pressure are slightly subnormal in amount, the consequent increase of the volume of blood in the heart calls into play greater power of contraction. In a similar way this law explains the capacity of the heart to accept widely varying amounts of blood from the venous system, and to increase the amplitude of its strokes so as to pump the whole increased volume from the venous side over into the arteries. In the main the formulation, as Starling states it, is merely qualitative and not developed in terms of cubic centimeters per kilo nor in millimeters of venous pressure. His conception is that, practically speaking,

the stroke volume is determined by the venous return and pressure, and that it is a widely varying function even in the normal individual under uniform conditions.

The behavior of the heart in the heart-lung preparation appears on the whole to be quite different from that which the preceding pages have given us good reason to believe prevails in the normal living man. While this technique throws much light on the inherent capacities of the heart, it affords also an illustration of the errors resulting from neglect of the doctrine established by Pawlow in his *Work of the Digestive Glands*, that the behavior of an organ can only be inferred with certainty from observations made while it is functioning in the body of a living, healthy, happy, unanesthetized animal. As Haldane (1922) expresses it, "The various activities of a living organism can not be inferred in isolation from one another, since in the living body organic regulation dominates them." Thus "preparations from the bodies of animals" and experiments on "fragments of animals" are often essentially misleading.

Starling gives a definition of tonus which seems to the reviewer to be merely a rhetorical circle. It is the "fitness of the muscle fibre," and its measure is the "energy set free at each contraction." He considers it as a condition largely independent of the extent of relaxation and contraction and correspondingly lacking any necessary relation to the size of the heart's chambers at the time. This view is quite different from that which the volume curve reveals, and different therefore from the usual meaning of tonus in respect to striated muscle and to such hollow organs, analogous to the heart, as the stomach, bladder and blood vessels. Tonus in general is best defined as the height of the coefficient of elasticity; and hence the degree of resistance to deformation.

The conditions in experiments on the heart lung preparation are abnormal in the entire elimination of the cardiac reflex nervous control, and in the replacement of the influence of the arteriomotor and venopressor mechanisms, the arterial resistance and pressure and the venous return and pressure, by arrangements of glass and rubber. They are also abnormal in that, while the blood is aerated in the lungs and thus adequately oxygenated, it is over-ventilated as regards CO_2; for the only considerable source of CO_2 in the experimental arrangement is the heart itself. Thus not only is the CO_2 content of the blood reduced very low, but the CO_2 ratio ($H_2CO_3 : NaHCO_3$) and the H-ion concentration are abnormally reduced. The heart is thus rendered abnormally resistant to distention and abnormally high venous pressures are usually necessary. (Henderson, 1908; Jerusalem and Starling, Kaya and Starling, Moore, Patterson, Mansfeld, Mathison, Itami, Hooker, 1912.) On the other hand, the arrangement has distinct advantages in the ease of adjustment of arterial resistance and venous supply.

When we turn to the detailed data of Starling's experiments, and compare the venous pressures employed and the stroke volumes obtained with those of a normal man or animal, we find that the blood flow in cubic centimeters per kilo body weight (figures which unfortunately are not calculted in the originals) are not only very variable in different experiments and papers, but also are often so abnormal that they would be entirely incompatible with normal life. Thus in many experiments the stroke volumes figure out to less than 0.5, or 0.4, or even 0.3 cc. per kilo body weight at the normal effective venous pressure of 5 or 6 cm. water. They are indeed larger, but often less than 1 cc. per kilo, at the relatively high pressures of 8 to 10 cm.; and in many experiments they do not amount to as much as 1.5 cc. per kilo body weight until the enormous and abnormal venous pressures of 20 or 30 cm. are reached; and then the heart breaks down or, as Starling puts it, is fatigued, although the stroke volume and the work done by the heart are not greater than it maintains for years during normal life. On cats a maximal stroke volume of 1 cc. is found. The body weights are not given, but if we assume 3 kilos, the stroke volume and circulation rate would figure out to quantities which would be even smaller (in cubic centimeter per kilo body weight) than in the dogs' hearts studied.

We have here then the same phenomenon as that exhibited in the experiment of Howell and Donaldson above quoted. The essential points against all such data are two: *1*, The normal effective venous pressure in a small animal during rest is only 5 to 7 cm. water. *2*, If the stroke volumes at such pressures during life were less than 0.3 cc. per kilo body weight, the coefficient of oxygen utilization would rise to 100 per cent, and the man or animal would die of asphyxia; unless, as Tigerstedt has pointed out, Bohr was correct in claiming that there is normally a large pulmonary oxidation.

In fact, however, it is exceedingly probable that such observations are simply errors due to faulty experimental technique, and that the hearts were abnormally resistant to distention owing to their perfusion with blood in which the CO_2 content was abnormally low. That this was the case is clearly proved by the experiments of Lovatt Evans (with Starling) in which the blood gas analyses show that the CO_2 content of the blood was reduced to one-third or even a quarter of the normal. Henderson (1908) showed, and Jerusalem and Starling confirmed the observation, that extremely acapnial blood has this effect upon the heart, although in later work Starling and his collaborators have sometimes neglected this condition.

In investigations which Henderson and Prince (1913) carried out upon the excised cat's heart the same small stroke volumes, 1 cc. or less, were observed at first in hearts perfused with diluted sheep's blood; but when this blood was not only oxygenated but also impregnated with at least 50 volumes per cent of CO_2, the stroke volumes were increased to 3 or 4 cc. for each ventricle at venous pressures of only 5 or 6 cm. of blood; and the hearts continued to beat in this way for hours. It was found that even a small amount of ether was deleterious, and in the best experiments sudden decapitation without the slightest prevous anxiety, pain or anesthesia, was employed before excision of the heart.

In their investigations on cats' hearts perfused with oxygenated and adequately carbonated sheep's blood, Henderson and Prince found that the left ventricle behaves in a manner in general accord with Starling's

law, but at a very much lower range of pulmonary venous pressures than those which one infers (if the left ventricle behaved at all like the right) from the papers of Starling and his collaborators. In the right heart, on the contrary, the maximum stroke volume (three times larger than any obtained by Starling and his collaborators even at abnormally great venous pressures and without the "fatigue of the heart" which they met) was attained at about 5 cm. pressure. Above this pressure all beats were maximal. Below this level the stroke volume varied with the pressure. The left heart was capable of taking more than the right heart was capable of sending. The general conception reached was that, while the left ventricle is the chief motor, the right ventricle is essentially the meter of the circulation. How this meter is operated and controlled is best shown in studies of the volume curve of the ventricles.

THE VOLUME CURVE OF THE VENTRICLES. Douglas and Haldane in the paper previously quoted have furnished strong evidence that the initial description of the volume curve (Henderson, 1906) affords an essentially correct picture of the behavior of the heart in a normal man. The general features of the circulation rate shown by this method differed, not so much qualitatively as quantitatively, from those found in most of the investigations upon animals quoted in the preceding pages. This result was due to the observance of certain precautions, without which the results of this method would also show the same lack of simple relation of heart rate and stroke volume to circulation rate, the same necessity for abnormally great venous pressures, and the same extension of Starling's law far above normal limits, which the investigators quoted in the two preceding sections have generally found under operative conditions. The precautions were prevention of acapnia, and assurance of a normal venous supply and pressure, as indicated by the upstroke of the volume curve, expressing the diastolic receptive relaxation and filling of the heart. A number of other investigators (Wiggers, Straub, deHeer, Socin, Schram) have studied the volume curve and have utilized it for important contributions to analysis of the heart's mechanics, normal and abnormal. Most of this work lies beyond the immediate scope of this review. The chief points to be here considered are concerned with the diastolic filling of the heart as the underlying condition determining the stroke volume (Henderson, 1908, 1909; Henderson and Barringer).

Harvey's sole considerable mistake (so far as we yet know) in describing the heart beat lay in the statement that it is the contraction of the

auricles which fills the ventricles. The volume curve, on the contrary, demonstrates that the greater part of the filling takes place during the earlier part of diastole, the period immediately after the systole of the ventricles; the next following systole of the auricles usually adding very little blood to the ventricles, although having other important functions not here in question (Henderson and Johnson). Venous pressure, not the force of auricular systole, is the agency which distends the ventricles.

If the heart is capable of varying its amplitude of stroke tenfold, or even threefold, as has been held by Ludwig, Zuntz, Starling and others, it is essential to learn the controlling conditions. In the respiratory mechanism, in which very large variations do occur, the variations of tidal volume depend upon the innervation of the diaphragm by the phrenics and upon the intercostal muscles and nerves. Do the cardiac nerves exert a similar control over the amplitude of heart beat? Henderson and Barringer utilized the volume curve technique to show that the cardiac nerves have no such power over the heart, and that it is only through variations of rate of beat that the vagi and sympathetics influence the amplitude of beat and the stroke volume. When the rate is so rapid as to leave insufficient time for full strokes, stimulation of the vagi by slowing of the rate of beat and lengthening diastole, may allow larger strokes. At very rapid rates further acceleration induced by stimulation of sympathetic fibers, by abbreviating diastole, may leave inadequate time for relaxation and filling, and may thus decrease the amplitude of beat. Aside from such effects, however, the cardiac nerves have little direct influence upon the stroke volume, although Wiggers and Katz (1920) and Wiggers (1920) have found that the duration of the periods of the cardiac cycle may be influenced.

The relation, which the volume curve shows between venous pressure and stroke volume, is that the rapidity and extent of diastolic filling increases progressively from zero pressure up to an effective venous pressure about equal to that existing in a normal man or animal, that is up to about 5 cm. of water in the dog. At this critical value the stroke volume in dogs is about 1.5 to 2.0 cc. per kilo body weight, and makes practically no increase with further increase of venous pressure within physiological limits; during healthy life all beats are therefore of about maximal amplitude. Below the critical level lies the first stage of circulatory depression; in this state occur all the bewildering and at first sight lawless relations which have usually been found between stroke volume, rate of beat and circulatory rate. It is probable that

the circulation in a person who is ill behaves thus. The second stage of still less adequate venous supply and filling of the heart, and consequent fall of arterial pressure, is the essential circulatory feature of well-defined shock.

In general Wiggers and his collaborators have confirmed this conception of the dependence of the filling of the ventricles and their stroke volume upon venous pressure. Wigger's observations on hemorrhage (1910) are especially valuable analyses of these relations. Wiggers (1914) and Wiggers and Katz (1922) have attempted, however, to show that the critical venous pressure, that below which the stroke volume is not maximal but variable, is much above the normal effective venous pressure; and this would mean that the stroke volume in normal life is a widely varying quantity. Examination of their protocols and records shows that these observations were made on hearts which, like those in the experiments of Howell and Donaldson, Starling and others, were abnormally resistant to distention. At normal venous pressures the circulation rates were too small to provide the amount of oxygen which the body requires to support life—unless Wiggers is prepared to adopt the Bohr theory of a large consumption of oxygen in the lungs. Like a great part of all the evidence in the literature regarding blood flow, his experiments on this topic are misleading because made when the subjects were moribund.

The volume curve also demonstrates that the rate of relaxation of the heart in diastole, as expressed in the up-stroke of the curve, is quite as important a feature of the heart's behavior and effectiveness as a pump, as is the systolic contraction expressed in the down-stroke of the curve. It is essentially similar to the relaxation curve of a striated muscle in an isotonic contraction curve: very steep at first, a bend, and then a part approaching a horizontal line. Diastole is thus found to consist of a period of rapid relaxation and filling, and a period of diastasis (Henderson, 1906) in which the dilatation is much slower or even, when this period is prolonged, comes to a standstill. Diastasis may therefore be abbreviated by increase of heart rate without considerably diminishing amplitude of stroke. The extent of the systolic contraction also increases, and the volumes of blood in the heart at the end both of systole and of diastole decrease, with increasing rapidity of beat and the accompanying increase of tonus. Variations of the duration of diastasis afford the principal explanation of the fact that the normal human heart in such a subject as Douglas (see table 1, B) is capable of the same volume of stroke at 60 and at 150 beats per minute.

Rates of beat so rapid as to allow no time for diastasis, and even to cut into the period of rapid relaxation, necessarily involve an abbreviated amplitude of diastolic relaxation and a corresponding decrease of filling and of stroke volume. At such excessive rates of beat, although the product of stroke volume and the rate of beat, that is, the circulation rate, may for a time increase still further, a decrease must ultimately occur as the heart approaches a condition bordering on tetanus. The less rapid the diastolic relaxation of the individual heart, the sooner this condition must develop. If an old man's heart relaxes slowly, his capacity for physical exertion is thus limited (compare p. 189); for the circulation rate would not be accelerated proportionally to the pulse rate during exertion, even though the systolic contractions were still like those of youth.

There are distinct differences between the cardiac volume curves of the cat and dog, the two animals which have been studied and from which we infer the behavior of the human heart; in the cat diastasis is generally a comparatively slight feature at normal heart rates, while in the dog's heart it is usually a definite period. From these facts it may be inferred, in accord with the capacities of the two animals for exertion, that a dog's heart with increasing rate of beat merely abbreviates diastasis without decreasing amplitude of stroke, and thus increases the circulation rate: hence the dog's capacity for sustained exertion. In the cat, an animal capable of sudden and intense but only brief exertion, an increase of heart rate necessarily decreases amplitude of stroke, and can increase the circulation rate comparatively little.

The human heart certainly behaves in a manner equally characteristic for the species man; but, as its volume curves can not be directly recorded, we have to infer the shape of the curve, and hence the capabilities of the heart, indirectly. From the durations of systole and diastole at various rates of beat as measured in pulse curves, the writer has found (unpublished observations) that in some persons the shape of the volume curve may be plotted; indicating conformity to a uniform or "superimposable" type curve. Evidently the heart of a vigorous man, which has a duration of systole of 0.2 to 0.25 second and is capable of beating 150 times a minute, or 0.4 second per beat, without considerable abbreviation of the duration of systole or lessening of amplitude of stroke volume, is an organ of very rapid diastolic relaxation and filling. The capacity of an athlete for intense and prolonged exertion must be founded in part upon the rapidity and extent of the up- and

down-strokes of the volume curve of his heart, and upon a long diastasis during slow pulse rates: a volume curve during rest shaped almost like a succession of mathematical root signs.

The claim that the volume curve can not be a true index of the stroke volume (Gesell) is refuted by the fact, established by Rothberger, that the circulation rate calculated from a volume curve, and that from a stromuhr inserted in the aorta, with a reasonable allowance for the coronary blood flow, give nearly identical measurements of the circulation rate. (For the special type of tambour required to record the volume curve without appreciable error, see Henderson and Barringer.)

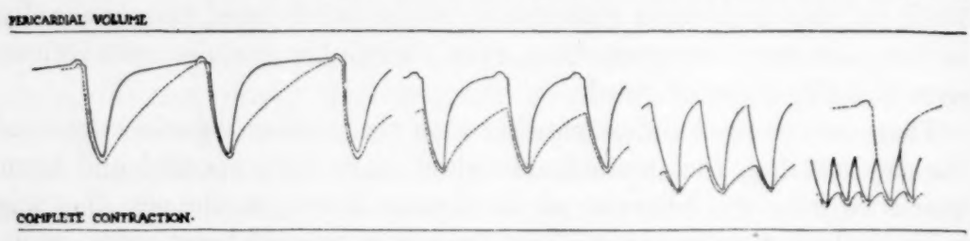

Fig. 1. Typical volume curves at slow, medium and rapid heart rates, with the corresponding changes of tonus, and of systolic and diastolic volume. The lower dotted curves illustrate the effect of a slow diastolic filling, either from slow relaxation, or low venous pressure. The upper dotted curve at the right illustrates the conception of a uniform, superimposable, normal volume curve. If the first three beats at the left indicate a circulation rate of (say) 1.0 liter per minute, the next would give 1.6, the next 2.5, and the rapid beats at the right 3.0 liters per minute. The corresponding dotted curves with slow diastolic relaxation and filling indicate circulation rates of 1.0, 1.0, 0.9 and 0.8 liter per minute. To see the similarity of volume curves to isotonic muscular contractions, look at them upside down.

The volume curve has the same form as an isotonic muscle curve, as Frank first showed. This indicates that in the contraction and refilling of the heart, the volume of blood in the ventricles varies directly as the length of the cardiac muscle fibers. On geometrical grounds it has generally been held that the volume must vary as the cube of the length of the muscle fibers. This would of course be necessarily true, if all diameters varied proportionally; but such is not the case, and the heart would be a far less efficient pump if it were: in fact, the dorso ventral diameter may even increase during systole. If all diameters varied proportionally, the shape of the volume curve would be quite different from the isotonic form.

In some of the best records of the volume curve it was found (Henderson, 1908) that at various rates and amplitudes of beat the volume curves were longer or shorter arcs of a nearly uniform type curve

obtained during slow and full, or vagal beats. Wiggers and his collaborators have subjected this theoretical conception to a searching experimental critique, and have shown that under experimental conditions it does not hold at all precisely. Nevertheless in his recent discussions of the mechanics of the heart, Wiggers seems to keep this conception as a background, and to regard it as the underlying principle of normal cardiac behavior, as the reviewer believes it to be. It is probable, however, that in spite of every precaution in maintaining vitality in an experimental animal, even the best volume curves obtainable fall short of the normal steepness and extent of the diastolic up-stroke; for a dog must have the capacity, as a man certainly has, but as only the most spike-like (vagal) strokes in the volume curve would allow, to increase the rate of beat to 2.5 or even 3 times the resting rate without decrease of amplitude of stroke.

Some years ago Prince and Henderson devised a cardiometer with a soft rubber bag inside it fastened at the edge of the window. The apparatus could be placed over the heart and the thorax again sewed up without leaving a pneumothorax. The air tube connected with the space between the bag and the cardiometer was led out through the body wall without leak. The work was not published because, after the animals had come out of anesthesia with the cardiometer inside of them, they were not vigorous enough to do more than to stand or walk slowly, instead of running on a tread mill as intended. As they were unfit for vigorous exertion after so large an operation, it was soon necessary to anesthetize and kill them. The volume curves of the ventricles recorded from them, however, were in all essential features identical with those previously published.

THE VENOPRESSOR MECHANISM. One of the principal contributions which recent years have brought to our topic has been the general recognition of the importance of the volume and pressure of the venous blood stream returning to the right heart (Henderson, 1908, 1910; Mann; Dale and Laidlaw, Dale). The conditions, whatever they are, underlying the venous return may be conveniently termed the venopressor mechanism. It is the volume and pressure of the venous return which, combined with the diastolic receptive relaxation and distensibility of the right ventricle, determines the stroke volume. It is this factor in the circulation rather than any variation in the heart itself, which determines what clinicians, after feeling the pulse, term "the force of the heart beat." What is the nature of this mechanism?

Ludwig and his pupils, and following them all physiologists down to recent years, assumed without the slightest suspicion of a possible error or omission that regulation of the circulation falls almost wholly under the control of only two mechanisms: the cardiac and the vasomotor. If the heart was beating vigorously and "blood pressure" (meaning arterial pressure, the use of a false term illustrating the error we are discussing) was at a normal level, then the circulation was assumed to be normal. In fact, however, the venous return to the heart is, as first shown in connection with studies on the volume curve (Henderson, 1908 et seq.), a factor in the circulation largely independent of arterial pressure and under a control distinct from that of the vasomotor (arteriomotor) nervous system.

This mechanism is as yet incompletely analyzed, but seems to be located in the capillaries and venules, and is apparently, like respiration, largely under chemical control. Like respiration also, it is very delicately adjusted and is easily depressed by anesthesia (Henderson, Haggard and Coburn), over-ventilation (Henderson, 1908 et seq.), cold (deAlmeida), circulatory obstruction (Janeway and Jackson, Erlanger and Gasser), hemorrhage (Henderson and Haggard, 1922), histamine (Dale and Laidlaw), the products of tissue destruction (Cannon, 1922), and other even slightly depressive conditions. It is extremely probable from such investigations as those of Romberg and Pässler and Macallum (for literature see Hewlett, 1919) that in the circulatory depressions of acute disease it is the venopressor mechanism which is usually involved, and neither a cardiac depression nor a vasomotor depression like syncope.

The vasomotor (arteriomotor) mechanism is in fact usually extremely resistant to depression, as has been conclusively demonstrated by W. T. Porter.

In accord with this are the facts demonstrated in this laboratory that the well-recognized procedures for increase, and maintained increase, of activity of the vasomotor mechanism, such as direct and reflex nerve stimulations, adrenalin, nervous excitement, etc., have only a momentary effect, but no considerable continuing effect on venous pressure; while the conditions above mentioned as depressing the venous pressure and return are compatible even with excessive vasomotor activity.

Owing to the valves in many of the systemic veins, bodily movements exert a pumping action and propel the venous blood toward the right heart. The inspiratory movements of the thorax and the contraction of the abdominal muscles in deep breathing have a similar

effect. A general vasoconstriction by increased activity of the adrenals—if, as Cannon (1911) holds, this occurs during fear or anger—may temporarily increase the venous flow and pressure. A splanchnic constriction under the increased innervation of excitement or exertion may act similarly. But all of these factors together appear to be quite insufficient to produce the gradually rising and sustained venous pressure, and the augmented flow to the right heart which, coincident with an accelerated pulse, produce the increased rate of circulation during muscular work and augmented respiratory metabolism.

The most hopeful field in which to look for the now unknown essential factors in the venopressor mechanism, apart from the vasomotor nervous control of arteries and arterioles, is that of the rapidly accumulating knowledge of the independent contractility of capillaries and of such circulatory effects as those of histamine (Dale and Laidlaw, 1919). Thus Dale in his Harvey Society lecture (1919), in speaking of histamine shock, shows that the failure of the circulation is due to relaxation of capillaries, stagnation, decreased venous return, inadequate diastolic filling of the heart, and consequent failure of systolic output. As Krogh also (1919, 1922) truly says in speaking of shock as due to capillary dilatation: "Nothing can be more striking than the contrast between . . . . arteriole dilatation and capillary dilatation respectively." These statements are essentially similar to those of the reviewer (Henderson, 1908, 1910).

Many of the investigators quoted in this review have recorded their opinion that the circulation rate is correlated with the degree of muscular activity, oxygen consumption and CO_2 production. In general there is a tendency to recognize that CO_2 is a more potent influence (both through its influence upon H-ion concentration, and through specific qualities) than is oxygen in the regulation of the circulation, as Haldane and others have shown it to be in the adjustment of respiration. The evidence will therefore be here briefly cited which indicates that the amount of CO_2 in the tissues and venous blood is the controlling factor in the regulation of the venopressor mechanism (whatever its nature) during the activities of normal life.

The writer has had peculiarly favorable opportunities to make observations on the rise of venous pressure coincident with increase of CO_2 in the body in normal men, while testing so-called oxygen helmets for the U. S. Bureau of Mines. If the alkali cartridge is defective, the exhaled CO_2 accumulates in the apparatus and in the man's body while he breathes an atmosphere rich also in oxygen. A marked rise of

venous pressure and dilatation of veins always result. The same extent of venous dilatation, i.e., relaxation of the veins themselves, occurs in a Turkish bath; but under mere heat the rise of venous pressure is absent. Studying men in the laboratory, Henderson, Prince and Haggard found that the measurement of the venous return in man is most effectively and significantly made in the head down position. When thus observed after forced breathing the venous column was lowered 8 to 11 cm., an amount corresponding to the depression found by the same method in patients after anesthesia and operation. On the other hand venous pressure was markedly elevated alike after exercise and after inhalation of 6 or 7 per cent CO_2. The effects passed off slowly.

Schneider and Truesdell have found on eleven human subjects that when the alveolar CO_2 was kept at 7 per cent (normal 5.0 to 5.7) and ample oxygen supplied, the venous pressure was increased 74 per cent. Capillary and arterial pressures also rose, while the volume of the hand and the blood flow through the hand decreased. When normal air was again breathed, venous pressure returned to normal much more slowly than arterial and capillary pressures. The authors say that "the rise of capillary and venous pressure . . . . suggests an increased return of blood to the heart, and therefore a well-defined increase in the minute volume of blood flow from the heart. Contrary to this indication we find the heart output per beat . . . . never clearly increased." Liljestrand also has found that in normal subjects inhalation of CO_2 does not augment the circulation rate.

The fact that venous pressure may be distinctly increased in normal subjects, without increase of stroke volume, seems to accord with the view that the normal venous pressure is at or above the critical value, and is therefore sufficient to produce maximal beats. On the other hand, in patients depressed by anesthesia and operation, Henderson, Haggard and Coburn have obtained marked and rapid increase of the circulation, particularly of the venous return with apparently also a greatly increased stroke volume and striking changes in the skin capillaries under CO_2 inhalation.

Henderson and Harvey attempted to analyze the problem of the nature of the venopressor mechanism, but the argument is too complex to repeat here. It was in part hypothetical and does not appear to have been convincing to others. In their experiments abolition of vasomotor control was obtained by section of the spinal cord in curarized dogs and was evidenced by enormous lowering of arterial pressure,

with but slight or no change of venous pressure. Electrical stimulation of the cord restored and maintained arterial pressure, but affected venous pressure only slightly. In a curarized dog stimulation of the central end of the sciatic induced a great rise of arterial pressure, but only a slight and temporary effect on venous pressure. In decapitated cats a slow injection of adrenalin raised and maintained arterial pressure but venous pressure was affected only temporarily and returned to a low level even during continuation of the injection. On the other hand, in decapitated cats maintained by insufflation of oxygen, the addition of 15 per cent CO_2 produced only slight effects upon arterial pressure or the heart, but induced and maintained an enormously high venous pressure. There was no indication that the heart was injuriously affected, but rather the contrary. This experiment, in the reviewer's opinion, shows that the mode of coördination between the volume of the venous return and the respiratory metabolism is essentially through the peripheral effects of CO_2 or, less probably, (as arterial pressure was not influenced) through spinal centers. But the problem is only in its beginning; for Krogh (1919, 1922) finds that the respiratory gases in physiological amounts have no distinct effects upon capillaries. His observations are, however as yet, chiefly upon the frog. Mall's observations are usually quoted as showing that the additional blood in muscles during work is drawn from the splanchnic area. But this explanation becomes less and less satisfactory (Henderson and Harvey), or even tenable (Burton-Opitz).

Mathison, Hooker (1918, 1920, 1922), Fuhner and Starling and others have worked on this and closely related topics. Their results are in general not very concordant with the conception of the nature of the venopressor mechanism above indicated (Henderson, Mann, Dale, Krogh) nor with each other, except on the broad fact which every one now admits that CO_2 in excess and CO_2 deficiency, whether acting directly or through the H-ions of the blood, have powerful influences on many factors in the circulation.

Dale and Evans have recently found that, in cats either decapitated or under urethane or paraldehyde, excessive ventilation induces a marked lowering of arterial pressure; but that this effect does not occur if the lungs are equally vigorously ventilated with air containing CO_2 (human expired air). Venous pressure was, however, only slightly, if at all, affected; and they consider that the point of action is in the spinal vasomotor centers. They show that the effects are due to acapnia, and not to alkalosis.

In this connection attention may be called to the interesting experiments demonstrating the peculiar effectiveness of carbonic acid in contrast to other acids in its penetration of cells and influence upon protoplasm recently reported by Jacobs.

Whether the venopressor mechanism is some special mechanism or, as is still held by most investigators, merely a part of the general vasomotor mechanism, is a question for further investigation. Both experimental and clinical observations on man seem, however, to demonstrate that, both in the ordinary activities and work of human life and in the conditions of patients under anesthesia and operation, CO_2 is the hormone somehow regulating the venous return.

Observations by x-ray. The x-ray shadow and photograph, and the orthodiagram have not afforded such complete and easily interpreted and measured data as might at first have been expected; and the limits of space here allow mention only of points directly concerned with our topic, with no attempt at a general survey of the large literature of x-ray observations on the heart.

It is a significant fact that no observer has reported, and we may be sure therefore that there do not exist, such variations in the amplitude of pulsation of the heart's shadow, between bodily rest and muscular exertion, as would be expected if the amplitude of the stroke volume is subject to a several fold variation. On the contrary so far as the evidence goes, it indicates on the whole a stroke volume of nearly uniform amplitude during rest and exercise.

Against the theory of much larger heart beats during exertion than during rest is also the fact that the shadow is generally slightly smaller (Dietlen), not only immediately after, but even during, muscular work (contrary to the initial observations of Nicolai and Zuntz, and Zuntz and Schumberg) than it is during rest. No larger beats should therefore be expected during work.

In the heart shadow, as Dietlen also says, "at the end of the systolic contraction the ventricles appear for an instant to stand still; . . . and at the end of diastole one sees (when the breath is held) that for a relatively long period the ventricles stand quite still." This first pause is a confirmation of the appearance of the volume curve (the blunt end of the spike) at the end of systole. The second and longer standstill is a direct demonstration of diastasis as a normal period at the end of diastole during slow pulse rates in man.

Even in the shadow of the human heart the maximum extent of movement of any boundary line is only 6 mm., and it is correspondingly

less in smaller animals. As the heart does not contract symmetrically, it is extremely difficult to transform such changes of area into values in cubic centimeters. In spite of this difficulty, Meek and Eyster have utilized the shadow of the dog's heart to estimate the variations in stroke volume after hemorrhage, and find practically no decrease in the shadow, but a distinct decrease by the volume curve, under a moderate blood loss. They have also applied the method to the behavior of the heart during an artificially produced plethora, and find an increase both of diastolic volume and of stroke volume in accord with Starling's law. Exercise, they find (1923), may increase the stroke volume by 20 per cent. But this amount is so slight that these observations really weigh strongly against the theory of a two or three hundred per cent variation of stroke volume. Increase of stroke volume coincident with decrease of diastolic size occurred in some cases: a fact incompatible with increased length of fiber as the cause of the increased stroke.

In like manner, Bruns, in a recent study of the heart's shadow of forty-eight human subjects during rest and muscular work, finds that in 75 per cent of his cases the heart is smaller after exercise than before exercise; and that during work it is larger in 15 per cent of his subjects, smaller in 25 and variable in the remainder. Even an increase of 10 to 40 mm. arterial pressure, and 10 to 50 beats per minute causes a maximal increase of shadow area of only 3.3 to 5.5 per cent. From these observations Bruns concludes that the human heart in the normal body does not behave as Starling and other investigators, working on animals under experimental conditions, have generally believed. He says that there is "a fundamental distinction between experimental and clinical observations" (meaning by "clinical observations" those made under the conditions of real life) regarding the behavior of the heart, for in order to produce 3 to 4 times as large stroke volumes during work as during rest, as these writers hold to occur, distinct increase of diastolic size would be necessary. That he would have found such an increase, if it had existed, Bruns shows by the fact that any decrease of venous return, as in Valsalva's experiment, is seen in a marked decrease of the area of the heart's shadow.

In regard to the critically important point thus demonstrated, it is noteworthy that Starling in his Linacre lecture (p. 25) admits that the increase of size (i.e., greater distention of the heart), which is necessary to call the "law of the heart," into operation and to produce larger strokes during muscular work, is "only temporary;" and he has

therefore to invoke increased arterial pressure and "a more abundant flow of blood through the vessels supplying the wall of the heart" to maintain the supposed increased extent of systolic contraction thereafter. This statement, however, to a large extent concedes the dissimilarity of behavior of the heart in the heart lung preparation and in the living body, and leaves little for the "law of the heart" to do in normal life.

PRINCIPAL CONCLUSIONS

Convincing evidence from a wide range of sources indicates that in vigorous men and other mammals of all sizes the stroke volume of the heart is a nearly constant quantity for each individual. Both during rest and work it is of the order of magnitude of 1.5 to 2 cc. per kilo body weight. Since this conclusion is, however, particularly as regards the stroke volume during rest, distinctly opposed to the opinion heretofore held (which assumed a variation of stroke volume of 200 to 400 per cent, or more), the following points of evidence upon which it chiefly rests deserve emphasis:

There is general agreement among investigators that during muscular work, and a high respiratory metabolism, stroke volumes of this order of magnitude are attained.

During rest the average oxygen utilization from the whole blood stream is, however, as we are now learning, much lower than was formerly believed, and the blood stream, or circulation rate, is correspondingly larger than had been inferred. This is strongly indicated by the newer evidence here reviewed. The oxygen utilization amounts to only 3 to 4 volumes per cent, or to a coefficient of 0.16 to 0.2 instead of 0.3 or more as generally held heretofore. With this fact established, there appears to be no other possible conclusion except that the stroke volume during rest is correspondingly larger than has been heretofore generally believed; and that it is of essentially the same volume during rest as during work. In other words, the stroke volume in a normal man or animal is practically a uniform quantity (within 20 or 30 per cent) during all the ordinary activities of life. The circulation rate is therefore nearly proportional to the pulse rate.

Reverting to views supported long ago by Hering and by Vierordt, but more recently neglected, it is here shown that in vigorous animals of various sizes the pulse rate and the circulation rate (measured in cubic centimeters per kilo body weight) vary, just as does the respiratory metabolism, in direct proportion to the surface : mass ratio; for the oxygen utilization and the stroke volume per kilo are nearly the same in mammals of all sizes.

The conditions determining the venous return, the so-called veno-pressor mechanism, are regulated by the CO_2 content of the tissues and venous blood. This mechanism and the regulation of the heart rate (the latter not here discussed) are the factors which adjust the circulation rate to the energy expenditure and respiratory metabolism during the various activities of normal life.

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THE FUNCTION OF THE VESTIBULAR APPARATUS

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The vestibule, as distinguished from the cochlear or auditory portion of the internal ear, is a circumscribed peripheral receptor present in all vertebrates from the Ostracoderms of the middle Ordovician period on to the present. It includes the sacculus, lagena, utriculus, otoliths and semicircular canals with their ampullae. Its form changes somewhat with the type of animal chosen for study, the ampullar and canal portion being represented in the Cyclostome Myxine or Bdellostoma by one canal with two ampullae, and by two canals in Petromyzon. In the Ichthyosaurs and Plesiosaurs, fossil reptiles of the lower Mesozoic (Triassic and later), it is much larger than in any extant form, the dimensions of the canals being in centimeters rather than in millimeters or their fractions, as is the case in present day vertebrates. The general anatomy of the vestibule is given in the papers of Retzius (1), Ayers (2), Bigelow (3), Stensio (4) and others. Shambaugh's (5) plates give the vascular supply of the vestibule of the fetal pig in detail.

Herrick (6) has given four criteria of a receptor; namely, the anatomical, the physical, the physiological and the psychological. The case for the vestibule may be examined briefly with reference to the application of these four criteria.

Anatomically, as well as physiologically, the vestibule belongs to Sherrington's group of proprioceptors. It is protected from direct contact with any ordinary agencies, or from direct excitation by any ordinary changes, in the external environment. The agencies which constitute its biologically adequate and normal stimulus must ordinarily arise within the body itself. The general structure of the vestibule suggests that the fluid contained within its various cavities and the otoliths in its saccule and utricle may act upon its specific nerve endings through the medium of a mechanical pressure generated by the inertia of the fluid or otoliths when the head is moved in any of the various planes of space.

Regarded from the point of view of physics, the idea that mechanical pressure may be the biologically adequate stimulus is supported not

only by theoretical considerations (7), (8), (9) but by actual experiment as well.

Physiologically, excitation of the vestibule gives rise to certain objective reactions of the eyes, the muscles of the limbs and trunk, and of certain viscera. Not all of these reactions are peculiar to excitation of the vestibule, but some combinations of reactions can be found which do appear to be peculiar to excitation of the vestibule.

Considered psychologically, the view recently taken by psychologists is that there is no mental quality arising from excitation of the vestibule that is discoverable on introspection. The general mental picture arising from any of the various experimental methods of excitation of the vestibule is rather to be considered as the integration of the various organic results of vestibular excitation and the mental consequences of these organic results than as something due to the vestibular endings alone (10).

The literature on the vestibule is enormous, probably including in all its phases about two thousand separate papers. A complete bibliography alone would require more space than can be devoted to the entire paper. The most complete recent bibliography of the subject is given by Griffith (11). Only a part of the physiological reactions arising from excitation of the vestibule can be considered at this time, without going very far into the vexed question of its central connections in the nervous system.

Although the early work on the vestibule was done on birds and mammals and even on the human subject, it seems best to depart from the traditional historical method of presentation and consider the effects of vestibular excitation or extirpation with reference to its comparative relationships. Although no true phylogeny of function can be given until the paleontologist and systematist have given us a more complete and logical account of vertebrate ancestry and descent than is now available, there is still a sufficient amount of difference in the reactions to vestibular excitation at various levels in the animal phylum to make such a method of presentation worth while.

The vestibule has been generally considered to be related to the maintenance of equilibrium. It is evident, however, that it cannot be the main receptive organ for the maintenance of equilibrium in invertebrates, since they do not possess it. A general account of the mechanisms in invertebrates has been given by Bethe (12), who points out that some of them maintain their normal position in space merely by their structure, that is, the distribution of the mass of the body with

reference to its center of gravity. Some dead organisms will float in water in the same position as the living organisms, and their position will be reversed when put into a fluid of a different specific gravity. Other invertebrates have so-called auditory pits containing grains of sand or other solid matter. Kreidl (13) washed the sand out of the auditory pit of a crustacean and replaced it with iron filings. The animal's movements could then be controlled by holding a magnet near it in the water. A considerable number of invertebrates have well developed otocysts, removal of which entails severe disturbances in locomotion. The literature is given by Fröhlich (14), Prentiss (15) and others.

Equilibrium in vertebrates. Passing over the long and unfilled gap between vertebrates and invertebrates, and even over the lower forms of what some consider vertebrates, we may take Amphioxus as the next type.

Amphioxus. Willey (16), in describing this form, states that "Besides lacking differentiated lateral fins, Amphioxus differs fundamentally from the higher Vertebrates in the absence of a cranium, of paired eyes, and paired or unpaired auditory organs" (p. 17).

"Amphioxus exhibits the characteristic vertebrate bilateral compression of the body in a very typical manner. It is obvious that such a shape of body is highly unfavorable for the maintenance of the equilibrium except with the assistance of some special mechanical and sensory apparatus. Now in Amphioxus, the metapleural folds, whatever their exact function may be, do not serve in any way as balancing organs; and, as mentioned in the text, Amphioxus has no means of maintaining its equilibrium when not actually swimming" (p. 43–44).

It is perhaps because of the difficulty of maintaining a body of such form in equilibrium that the locomotion of Amphioxus is so irregular, —"a rapid, curiously irregular wriggle"—periods of swimming forward, sometimes upon the back, sometimes upon the abdomen in the position of ordinary fishes (17) being interrupted by somersault movements and backward swimming (18) until the animal settles down and burrows tail first into the sand (19).

Cyclostomes. Experimental removal of the vestibule of Cyclostomes has been done successfully but once. Ayers (2) removed the vestibule from Bdellostoma dombeyi and found no appreciable disturbances of locomotion. Some of the same considerations which apply to Amphioxus apply also to Cyclostomes. Although there is a somewhat rudimentary vestibule—whether primitive or degenerative does not make so much difference from our present point of view—the locomotion of

Cyclostomes does not partake of the character of the strong swimming fishes, and the whole motor mechanism—nervous and muscular, shows a less high stage of development. Like Amphioxus, Bdellostoma has no fins, and its body is more like the cylindrical Balanoglossus than like the bilaterally compressed Amphioxus. While it has the sense organs for the perception of the change of aspect of the head in space, it has no paired effectors or fins which may react in a special way to excitation of the vestibule. As Willey points out, the maintenance of equilibrium is easier when the body is cylindrical than when it is bilaterally compressed, as in Amphioxus. Bdellostoma swims with eel-like movements of the body, and when at rest on the bottom, curves some part of the body, usually the tail, to one side or the other to keep it from rolling over.

Selachians. The relatively large size of the vestibule, and the fact that the soft cartilage in which it is embedded makes operative approach easy, have been among the reasons why the Selachians or Elasmobranch fishes have been favorite subjects of experimentation. The methods of experiment have varied from complete removal of one or both vestibules, section of the eighth cranial nerve, removal of the canals and ampullae without injury to the utricle, removal of the utricle without injury to the ampullae, exposure and mechanical excitation of the otolith of the utricle, and testing the reactions of the fins and eyes to a change in position of the head when the vestibule is intact. Most of the observations have been made upon some genus of the dogfish and upon rays. All three canals and the utricle and the saccule are well developed in Selachians, and we have for the first time in the vertebrate phylum, a fully developed vestibule with all its parts as it exists in higher vertebrates. Paired fins are also present in Selachians, and we have again the first complete mechanism for the maintenance of the equilibrium of a bilaterally compressed vertebrate body—sensory mechanism, central nervous system and effectors which may act as balancing organs. The maintenance of the normal posture of fish requires some mechanism, as Manoyer (20) showed that fish swim in labile rather than stable equilibrium.

Such a balancing mechanism—a receptor, a central system and the effectors—fulfills Goltz's (21) conditions, and, although found for the first time in living vertebrates in the Selachians, exists in a modified but physiologically adequate form in such free-swimming invertebrates as the crayfish and the lobster. But it is well to state here that the vestibule does not constitute the only receptor which is concerned with

the maintenance of the normal position of any vertebrate in space. Other proprioceptors and the exteroceptors must be taken into account, and the maintenance of equilibrium is an act requiring a high degree of correlation of response (22) and a highly developed mechanism of integration in the central nervous system. It is only by keeping these things in mind that we may guard against either of two errors—attributing too great an importance to the vestibular mechanism, or denying its efficacy altogether.

The reactions of the eyes and fins of the dogfish with intact vestibule when rotated about any one of the three axes of the body— longitudinal transverse or dorsoventral—are too well known from the work of Lee (23), Maxwell (24), Lyon (25) and others to require more than a brief mention. It has been found that stimulation of the ampulla of one anterior canal causes the eyeball of the same side to roll upward and the other downwards, but the direction of rotation of the eyes about the anteroposterior axis is reversed. When the anterior canal is stimulated, the anterior pole of the eye of the same side rises more than the posterior; when the posterior canal is stimulated, the posterior pole of the same side rises more than the anterior. The direction of rotation of the opposite eye is always the reverse. Stimulation of the ampulla of the horizontal canal causes the eye of the same side to roll straight forward, and the other eye straight backward. Maxwell differs slightly from this account. According to him, the eyes of both sides rotate forward on their visual axes when the ampulla of a posterior canal is stimulated, and backward when the ampulla of an anterior canal is stimulated. According to Lee, the direction of rotation of the two eyes about their visual axes is opposite; according to Maxwell, it is the same when the ampulla of the anterior canal, for example, is stimulated.

Lee particularly, and possibly Maxwell, assumed that, in rotating a dogfish about any of the axes of the body, the ampullae and not the otoliths were stimulated. Breuer (26) had assumed that the canals and ampullae were concerned with the perception of movement in curved lines, i.e., angular acceleration, and that the otoliths were concerned in the perception of movement in straight lines, i.e., linear acceleration. This view was widely accepted, although no direct proof of its correctness had ever been given. In a later paper, Maxwell (27) described the reactions of a dogfish to rotation when the ampullae of all six canals had been removed without injury to the utricle. All

the compensatory movements of the eyes persisted after such removal of the ampullae, except those following rotation of the animal about its dorsoventral axis, i.e., in the plane of the horizontal canals. It seems clear, from Maxwell's results, that the otoliths are concerned, along with the ampullae, in the perception of angular acceleration.

The converse of this state of affairs,—reaction of the ampullae after complete removal of the utricular otoliths—was also tested out. When the utricular otolith is removed without injury to the ampullae, all the compensatory movements of the eyes in response to rotation of the animal about any one of the axes of the body persist.

After removal of the ampullae, with conservation of the otoliths, the compensatory movements of the eyes, although prompt, are noticeably slower than when the vestibule is intact. If seized while in the water, the animal strongly resists the attempt to turn it back downward; but one feels that this resistance is neither as prompt nor as strong as in the intact animal (27). In swimming there is a tendency to sway from side to side about the longitudinal axis like a boat insufficiently ballasted. When the otoliths alone are removed, with conservation of the ampullae, the compensatory movements are slightly slower than in the intact animal. Swimming is apt to be accompanied by a slight rocking movement from side to side; and if turned back downward in the water, the animal rights itself promptly, but may turn almost or completely over before coming to rest in the normal upright position.

The otolith of the utricle is more easily accessible in the shovel-nosed ray (Rhinobatus) than in the dogfish. It may be exposed and stimulated mechanically in situ, after removal of all the ampullae. Maxwell (28) found that "pressure on the right side of the otolith of either ear produces the same eye movement which results from rotation of the body to the left about its longitudinal axis," i.e., the right eye is depressed and the left rolled upward, "and that pressure on the anterior side of the otolith produces the same movement of the eyes which results from tilting the head upward,"—the eyes are rotated forward about their visual axes. It is the displacement of the otolith and not the weight due to the otolith which is the actual stimulus, and it is the direction of the displacement which determines the direction of the compensatory movement.

Maxwell's conclusions are that the assumption of a sharp differentiation of function between the otolith-bearing portions of the otic labyrinth and the semicircular canal portion is not justified by the facts.

The two parts of the labyrinth reinforce each other, for the reactions produced by either one alone are slower and less vigorous than when both sets of organs are intact. The two parts may not have identical functions, however, since response to rotation in a horizontal plane is completely lost after removal of the ampullae alone.

Removal of all ampullae and the otoliths of both utricles has the same effect as complete destruction of the vestibules or section of the eighth cranial nerves.

Some investigators have reported negative results from complete bilateral or unilateral destruction of the vestibule, but more recent work tends to show that there is a definite train of symptoms following such a lesion. All compensatory movements of the eyes and fins to rotation of the animal about any axis of its body are completely and permanently lost after bilateral lesions. The animal swims indifferently in the back upward or belly upward position. A weak animal comes to rest on the bottom of the tank on its side or back, but a vigorous animal will right itself on reaching the bottom, the reaction being due, in Maxwell's opinion, to the sense of touch. As he expresses it, the geotropic responses of the animal are lost, but the stereotropic responses are retained. Some degree of recovery may occur, but there is always some disturbance when the fish is made to swim rapidly, as a rule.

The effects of unilateral lesion are less severe. The eye of the injured side turns downward and the eye of the sound side turns upward 20° to 40°. The body is curved markedly to the injured side. In swimming, the fish may roll to the injured side. Normal swimming seems possible, but disturbances of locomotion, particularly when the eyes are closed, are very apt to appear. The displacement of the eyes is permanent as long as the animal lives—two weeks in some cases. Compensatory movements of the fins and eyes are still elicitable on rotation in any one of the three planes of space, although often weakened and difficult to observe.

Considerable discussion has arisen as to whether the effects of vestibular lesions are due solely to the loss of a peripheral receptor or due largely to the irritative effects of the injury. Gaglio (29), König (30) and Breuer (31), the last using pigeons, have applied cocaine to the vestibule. Gaglio observed, in the Mediterranean dogfish, the same results after the application of cocaine as after anatomical removal of the vestibule. This strongly indicates that irritative processes play but little part in the effect of vestibular lesions in this form. Again,

one would expect about as much irritation from destruction of the ampullae together with their specialized nerve endings as from complete destruction of the vestibule. Yet Maxwell found that the reactions of the animal, after removal of the ampullae alone, differed from those of the normal animal only slightly. Whatever effects of irritation may have been manifested elsewhere, there were extremely few which were apparent in those reactions which we have come to look upon as characteristic of vestibular excitation. It is my opinion that the effects of irritation in connection with vestibular lesions have been greatly over-emphasized. One might make the same statement with reference to many other lesions of receptors or parts of the central nervous system.

One other permanent effect of bilateral vestibular lesions was brought out by Gaglio, and that is the loss of muscular strength following this destruction. Parker (32) also remarks that the muscle tonus of the animal is noticeably reduced after bilateral lesions. This can scarcely be due to any effect on the muscles themselves, but rather to the loss of afferent impulses normally concerned in the maintenance of tonus or the utilization of muscular strength.

Both Parker and Maxwell agree that the saccular otolith has little or nothing to do with vestibular function proper. Parker regards it as a part of the mechanism of hearing in fish.

Although Mach showed the physical improbability, even impossibility of actual currents of fluid in the semicircular canals, the hypothesis of stimulation of the ampullar nerve endings by currents set up in the canals has been very popular among otologists. Maxwell freed the horizontal canal for nearly its whole length, ligated it near its posterior end and, after cutting it, raised it so that its plane was vertical. Rotation of the animal in a horizontal plane, about the axis of the canal in its new position, was attended by the usual reaction to rotation. No possible currents could have been set up in the canal under these conditions, and it is difficult to see how any pressure could originate in the canal to be communicated to the ampulla. In the statement of the mechanism of excitation of the ampullar endings, Mach, Breuer and Crum Brown supposed that pressure arising from the lag of the fluid in the canals during rotation was transmitted to the ampullae. Implicitly, it was assumed that the pressure arising in the utricle from the inertia of its contained fluid would either not be transmitted to the ampullae or, if so transmitted, would not be effective in stimulating the nerve endings. When one considers the mechanics

of the vestibule, there is no anatomical or physical reason discoverable for such an assumption. And, in view of Maxwell's results, there seems good reason for believing that the normal mechanism of excitation of the ampullar endings is the transmission of pressure from the utricle to the ampullae. In any event, it would seem time to give up, once for all, the idea of fluid currents in the canals under any ordinary conditions. On the other hand, we have Breuer's (31) statement that when rotation is sufficiently rapid or violent to set up actual currents in the vestibule, the ampullar endings would be injured, and the cristae acusticae swept from their places.

The evidence now available would seem to indicate that both ampullae and otoliths are capable of responding to angular and linear acceleration, and that the two mechanisms work together in this function. The otoliths, because of their greater specific gravity (Maxwell), would have a greater inertia than an equal volume of fluid, and there is no reason to suspect that their displacement might not occur in either angular or linear acceleration. There is no reason to suspect that the fluid in the utricle would not lag in either angular or linear acceleration, and thus give rise to pressure somewhere. It seems extremely probable that the transmission of this pressure to the ampullar endings constitutes their normal and biologically adequate mechanism of excitation.

Teleosts. Experimental work on the internal ear of teleost fishes has not been as extensive or carried out in as much detail as in Selachians, but the results at hand, so far as they go, are in keeping with the results obtained from the study of cartilaginous fishes.

Bigelow (3) showed by dissection that the ear of the gold fish, Carassius auratus L., is essentially like that of Cyprinus, as described by Retzius. There are certain anatomical differences in the ear of Carassius as compared with the ear of a shark, one of which is the presence of two otoliths in the combined lagena and saccule of Carrasius. The wall of this sac, as Bigelow showed, is supplied by branches of the eighth cranial nerve. Many of the experiments on teleosts were done in the course of experiments on hearing, and the disturbances of equilibrium were described only incidentally.

Tullberg (33) considered that the ears of the bony fishes were not organs concerned in the maintenance of equilibrium, and that they had little to do with hearing. Their main function, in his opinion, is the perception of slight movements in the water, and particularly those arising from currents in the water. He bases his arguments on the

fact that bony fishes may, in time, recover almost completely from lesions of the internal ear. The immediate effects are therefore due to shock, and not to the loss of a particular receptor.

Parker (34) found that Fundulus heteroclitus, after section of both eighth nerves, lost the power of maintaining equilibrium when swimming rapidly, and swam in any position in spirals or even in circles. In his discussion of Tullberg's view, Parker (p. 201) admits that Fundulus may recover fairly well in a few days after the operation, so long as it swims slowly. But it invariably loses this power of maintaining equilibrium if made to swim rapidly in a large amount of water. The greatest length of life of any animal after operation was six weeks, but the effects were clearly observable throughout this period. Parker attributed the partial recovery of the animal and its facility in swimming slowly to increased use of the eyes. He admits that this is an assumption on his part, but there is much evidence drawn from the study of reactions in invertebrates to support such a view. Until this assumption is definitely shown to be untenable for bony fishes, Parker considers that Tullberg's conclusion is premature.

My own view is in accord with Parker's. The same arguments adduced against peripheral irritation and shock in the case of vestibular lesions in the cartilaginous fishes apply with equal force in the case of the bony fishes. It may be shown that the loss of any one sense does not entail any very severe permanent disturbances of locomotion in higher animals. One might conclude, therefore, that no one of these sensory mechanisms had much to do with locomotion. The argument should be carried a little further, however. If no one sensory mechanism has much to do with locomotion, it should be possible to eliminate all of them and still retain relatively unimpaired powers of locomotion. For if the whole is equal to the sum of all its parts, the whole effect should be relatively slight. Common experience points very strongly to the conclusion that the total effect is not relatively slight. Since Euclid's argument has now been subjected to criticism and analysis for some centuries without suffering serious damage, I am inclined to suspect that the fault may lie in some of our common assumptions concerning the functions of various sense organs rather than with Euclid's reasoning. The presumption is strong that some of the quantities concerned in physiological reasoning, e.g., the effects of removal of various sense organs, are really variables instead of constants, as Tullberg's line of reasoning assumes. The reason for this variation lies less in some undefined shock effect than in the compensation for the loss of one sensory mechanism by another.

Bigelow's observations on Carassius are in agreement with Parker's. The facility of maintenance of equilibrium when swimming slowly after loss of both internal ears was lost when the fish was made to swim rapidly in a large body of water. The effects are permanent.

Parker (35) found that the catfish Amiurus suffered loss of muscular tonus and the loss of the power of maintaining equilibrium after section of both eighth cranial nerves. Most of the time of such fishes is spent in lying on the bottom of the tank, often with the ventral side up. When they swim it is usually in a slow rolling way, and when driven to rapid motion, they swim in grotesque spirals.

Bethe (12) had previously found much the same effects in Perca fluvialis and Scardinius erythrophthalmus after vestibular lesions. After a unilateral lesion, Perca shows a respiratory effect on the injured side. There is no loss of synchronism of the two sides in respiration, but the gill covers on the injured side are not raised as high as those on the uninjured side.

Ewald (36) confirmed on the eel, Anguilla vulgaris, the loss of strength noted by Gaglio in the dogfish. There were also severe disturbances of equilibrium.

Batrachians. Anatomical conditions in the batrachian ear preclude such exact and detailed study of individual parts of the vestibule as is possible in the sharks, but, on the other hand, the development of limbs makes possible the observation of the effects of vestibular lesions upon animals which have reached the second stage in the development of the vertebrate locomotor apparatus. There is also a further development of the central nervous system. By means of the limbs, these forms maintain a fixed position when at rest on the surface of some solid object, and hence are the first vertebrates which may be rotated on the turning table in such a way as to show the effect of vestibular excitation upon the resting position. The batrachians include also forms which, although they retain their gills throughout life and live in the water, effect their locomotion by means of limbs; other forms which retain their gills during the early part of life only and then emerge from the water upon the land, and still other forms which become so specialized that, after undergoing metamorphsis, their mode of progression upon the land is by hopping or jumping rather than by walking or crawling.

Stewart (37) used a perennibranchiate form Necturus (Menobranchus) for experiment. He found that destruction of the internal ear on one side was followed by rapid movements of rotation of the body,

always to the injured side, about its longitudinal axis. The movements are apparently involuntary and without fatigue. If for any reason these movements cease, they can be started again by excitation of the animal.

Ewald (38) found that in Salamandra maculosa, there are only slight motor symptoms as a result of vestibular lesions. After a unilateral lesion the legs of the opposite (uninjured) side are raised abnormally high, while those of the same side may be dragged along the ground.

Laudenbach (39) removed the entire vestibule, unilaterally and bilaterally, and the otoliths alone in Siredon pisciformis. After unilateral lesions of the whole vestibule, the animal rotates rapidly about its longitudinal axis when swimming, turning always toward the injured side. At first it can not go forward at all without undergoing this rotation. The disturbances are more marked in young animals than in old. Adults recover sufficiently in three or four days to swim slowly without turning over, but not to swim rapidly.

Whether bilateral operation was done on the same day, or whether the second labyrinth was removed after an interval, severe and permanent disturbances of orientation followed, when the animal was in the water. The animal maintained its position on the ground or at the bottom of the tank well. It could not maintain its normal position at the surface of the water, but floated belly upward with the nose under water. Any recovery that may have occurred after removal of one vestibule was lost after subsequent lesion of the second, so far as deportment in the water was concerned, and little recovery was seen even after fifteen months. The difficulty in swimming was so great that the animal could not get to the surface for air, and the gills again began to grow if the animal was kept permanently in the aquarium.

No noticeable disturbances of movement or equilibrium follow unilateral or bilateral removal of the otoliths without injury to the ampullae.

The effect of unilateral and bilateral lesions of the whole vestibule in the frog is so well known from the work of Schrader (40), Ewald and others as to require no special comment here. There is torsion of the head and body to the injured side after unilateral operation, swimming in a circle to the injured side and turning to this side in jumping. The fore limb of the sound side is strongly extended as if the animal were bracing itself by it, while the fore limb of the injured side is strongly flexed.

Henri (41) found that torsion of the head partially or almost completely disappears after an interval of six weeks or so. If decerebration is done at this time, the original symptoms reappear in all their original intensity, and no further amelioration of the conditions is observed so long as the animals live. If decerebration is done first and the vestibular operation afterward, there is no improvement in the condition of the animal as long as it lives.

Streeter's (42) observations on the effect of unilateral or bilateral removal of the auditory pit and acoustic ganglion in the tadpole are of considerable interest in relation to the ontogeny of vestibular function. The fact that it is possible to produce at will practically a congenital absence of the auditory vesicle serves as a control for the experiments on adult animals, and has a direct advantage in the permanence, completeness and lack of injury to contiguous structures over operations on adult forms. And since it may be presumed that the various organs possess their greatest degree of adaptability during the formative period, such embryonic interference affords a most complete test of the power of functional adaptation for loss of a specialized receptor.

The larval frog passes through three stages in acquiring the facility to swim, which Streeter names as follows; *1*, The stage of non-motility —the first three days; *2*, the stage of spinal reflexes—fourth to sixth days; *3*, the stage of maintenance of equilibrium, sixth day to maturity. At the close of the first or non-motile stage, the structure which is to form the future auditory vesicle is visible and may be dissected out. The auditory vesicle never regenerates after its complete destruction, including the acoustic ganglion.

The larva makes no effort to swim in the first twenty-four hours, and it is only on the fourth day after the operation (about the sixth of larval life) that any significant difference in behavior is noticeable as a result of the lesion. At this time, when they, as well as the normals, are stirred up from their resting position on the bottom or against the sides of the dish, the operated individuals swim in spirals or circles. There is a tendency to swim with the injured side under, and the rolling movements which occur about the longitudinal axis are always directed toward the operated side. On reaching the bottom, they are able to direct their courses as the normals do. The characteristic disturbances in swimming become more marked in the next two days, but on the seventh day after operation many of the operated larvae may swim in a fairly direct course. On exciting them, the rolling

movements reappear. There is improvement from this time on, but the larvae always incline more or less to the injured side, and momentary loss of equilibrium is noticeable whenever they become excited.

Metamorphosis occurred at the end of the third month. No difference in attitude, whether at rest or in motion, could be made out in the operated as compared with the normal individuals after metamorphosis. Streeter thinks that the disappearance of the symptoms does not indicate any cure of the condition set up by the lesion, but that a slight defect is more difficult to recognize in the frog than in the tadpole. As a corollary, he points out that the maintenance of equilibrium in the tail-swimming tadpole is dependent upon a more delicately balanced mechanism than in the leg-swimming frog. It might be pointed out, also, that a more perfect set of peripheral effectors for the maintenance of equilibrium is present in the frog.

After bilateral operation, there was practically no difference to be made out in the appearance of the operated and the control larvae for the first three days. On the fourth day after the operation, they are decidedly less active than the controls, or than larvae with one auditory vesicle only removed. They make no swimming movements, but wriggle along on the bottom of the dish. Seven days after operation, they are smaller than one-sided or control specimens. They are symmetrical in form, but are less active and make only unsuccessful attempts at swimming. Twelve days after operation, any attempts at swimming resulted in a series of somersaults, after which they sank to the bottom in almost any position. There is great difficulty in feeding, and wriggling movements along the bottom are not as well executed as on the fourth and fifth days after operation. The larvae could not be carried much beyond two months of life, as they seemed unable to get food, and to go to the surface for air as normal larvae do. They were only about one third as large as the controls at this time, and had no more ability to swim than they had a few days after the operation.

One may remark that the severity of the effects of a bilateral lesion is much more than twice that of the effects of a unilateral lesion. This great difference in severity of effects seems difficult to account for on any other basis than the compensation for the loss of only one auditory vesicle by the other. And the larval form, while it compensates quite as perfectly as the adult for the loss of but one ear, is much less able to compensate for the loss of both than is the adult.

Laudenbach found no noticeable defects after removal of the otoliths only, with conservation of the ampullae, in the frog. Ach (43), however, reëxamined the question. He calls attention to Breuer's (26) analysis of the spatial relationships of the otoliths in the ear of the frog, and the general parallelism of each of them to the plane of some one canal. He confirmed Laudenbach's observations so far as any effects upon the attitude of the body or the usual movements of progression were concerned. Ach brought out, however, three effects of the bilateral removal of the otoliths. There are three reflexes,—the "Stirn" reflex, in which the frog assumes a position so that its body is concave toward the ground, supported only upon the tip of its nose and its hind feet; the shrieking reflex, which differs from the ordinary croak reflex; and the lid reflex of the eye. The first two are difficult or impossible of elicitation in normal frogs, while the lid reflex is usually present. After bilateral operation the first two, the "Stirn" reflex and the shrieking reflex, were much more easily elicited than before, while the lid reflex failed in progressive linear movements.

After unilateral lesions of the otoliths, the lid reflex is still elicitable at times. When the frog is moved up or down in a vertical direction, and particularly when it is moved downward, the lid reflex appears in the eye of the injured side. In linear movement from side to side, or backward and forward in the same plane, both eyes, or one only, may close, whether the otoliths are intact, or absent on one side. Ach never observed closure of the eye on the sound side only after unilateral operation. If only one eye closes when the otoliths of one side are absent, it is the eye opposite to that of the sound labyrinth. The relationship appears to be a crossed relationship. After bilateral removal of the otoliths, the lid reflex persists practically undiminished, *a*, when the frog is rotated in a horizontal plane about its dorsoventral axis; *b* upward or downward about a transverse axis; or *c*, from side to side about its longitudinal axis. Under conditions of rotation, the lid reflex must be due to excitation of the ampullae. He considers the failure of the lid reflex in progressive linear movements after bilateral removal of the otoliths as the most characteristic effect. He attempts to show that Breuer's idea of the perception of linear acceleration by the otoliths only is correct.

Graham Brown (44) investigated the effects of physiological excitation of the vestibule upon the respiratory movements of the frog. The effects of vestibular excitation are not peculiar, but are very similar to the effects arising from pinching the toes of one foot, and

apparently may all be comprised in the usual cycle of acceleration and augmentation of the respiratory movements. Bilateral removal of the otoliths does not affect the response to movement in a vertical direction, that is, to linear acceleration, but complete removal of both vestibules abolishes the response. Brown supposes that the ampullae may respond to movement in a straight line, and departs from Breuer's and Ach's views. Extirpation of both vestibules has no permanent effect upon the respiratory movements, although there is indication of some temporary loss of tonus of the muscles of the floor of the mouth.

Reptiles. The reptilian brain represents the highest type of generalized brain. The superficial layer of gray matter on the cerebral cortex has increased in amount, as compared with the batrachian brain (45) and there is some representation of the central terminations of the optic fibers in the cerebral hemispheres (46). In higher vertebrate phyla, there is development of the avian brain on the one hand characterized by the relative preponderance of the cerebellum, and the mammalian brain on the other hand, characterized by the relative preponderance of the cerebral hemispheres. The vestibule is enclosed in hard bone, so that sharply localized lesions of its various parts are not easy to effect, and the mode of reproduction renders the extirpation or transplantation of the embryonic vestibule more difficult than in some batrachians. The variations in body form, from the extremely elongated serpents without any limbs whatsoever, to the turtles with their extremely stable base of support for the body and long mobile neck, afford an opportunity for study of the effects of lesions of one peripheral sense organ upon various types of locomotion in one phylum, and upon various parts of the body as well.

Trendelenburg and Kühn (47) used the European swamp tortoise, Emys lutaria, for experiment. After unilateral operation, they observed torsion of the head to the injured side when the head was in the shell and bending of the head to the injured side when it was protruded. Slow progression on the land was not attended by any unusual disturbance. The torsion of the head and neck is permanent, but there is no turning to one side in progression. The swamp tortoise is more active in the water than on the land, and more marked disorders appear in swimming than in crawling. When at rest, the injured side is lower in the water, and in swimming there is movement in a circle to the injured side. Frequently the animal spins about a dorsoventral axis. It rights itself when placed back downward in the water.

Compensatory movements of the head are slower and eye movements more rapid in the turtle than in the lizard. The loss of one vestibule does not alter the reaction of the head to a change of position. If the visual field is kept stationary, both the rotation and the post-rotatory effects are obtained if the rotation is toward the injured side, but the after effect fails if the rotation is toward the sound side. This is a point of some interest, as it indicates that one vestibule has less capacity of response to rotation in either direction in these forms than it has in the human subject. If the visual field moves with the animal, the rotation effect fails when the rotation is toward the sound side.

Bilateral lesions are not attended by any unusual manifestation when the animal is at rest. The movements on land are slow, but not otherwise abnormal. The head moves back and forth without resistance when the animal is shaken. It rights itself when placed back downward on the ground, but may remain in the back downward position when swimming. It turns to one side or the other, and may even turn in a circle when swimming.

Van Rossem (48) had given, the year before, an exhaustive account of the vestibular symptoms in turtles. Our own observations (49) have been along the lines of the unilateral and bilateral extirpation of the vestibule and electrical stimulation of the ear. Our results on extirpation are in general agreement with those of Trendelenburg and Kühn. Along with the torsion of the head following unilateral operation, there is a displacement of the eyes such that the eye of the injured side is turned upward and the other downward. When floating at rest, the limbs of the injured side are flexed closer to the body while those of the opposite side are extended. Food is grasped accurately and securely after the first few days. The torsion of the head lasts as long as the turtle lives, eight months in the case of some specimens. Any decrease in the torsion occurring in the first months of recovery is lost after decerebration. The torsion may become even more marked than before.

The effects of bilateral operation are more severe. The animal floats level in the water, and Nanemys will float on its back without righting itself. Chrysemys, because of the peculiar shape of its body, will not remain on its back in the water at all. In swimming, Nanemys may go in a small circle, swimming on its side with the back directed toward the center, or it may spin about its dorsoventral axis and stop with all limbs strongly extended and its nose pointing almost straight upward.

Control specimens grasped pieces of fish placed in the enclosure readily and accurately. The body is held immovable and the neck and head are suddenly thrust out. The jaws close with a snap as the food is reached, and the head is quickly retracted. I have seen a turtle, Chrysemys, repeatedly grasp at food after bilateral operation, without ever touching it. The head was retracted after each failure and again thrust out, only to go to one side or the other or above or below the desired morsel. Although evidently hungry, the animal might finally give up the attempt to grasp the food and crawl away. The broad flat body of the turtle affords a secure basis of support, and the inability to grasp the food signifies that the animal is unable, even with the aid of its eyes and muscular sense, to control the rapid movements of the head accurately. These erratic movements of the head bring out sharply the importance of Crum Brown's statement that the function of the vestibule is to give information of the aspect or change of aspect of the head in space. The vestibule is a proprioceptive structure whose biologically adequate stimulus arises from the aspect or change of aspect of the head in space, from the aspect or change of aspect of no other part of the body in space. Its loss leads to centripetal ataxia.

Electrical stimulation of the ear of the turtle is easily accomplished (50). When the direct current from fifteen to twenty dry cells is passed through the head from one ear to the other, there is a movement of the body, brought about largely by the hind feet, so that the head is turned toward the side of the anode. The response persists after decerebration.

Loeb (51) brought out the important principle in the horned toad Phrynosoma, of the algebraic summation of optical and vestibular stimuli or, as he calls them, heliotropic and geotropic effects in the elicitation of compensatory movements during and after rotation. When the lizard is rotated, with ears intact and eyes closed, a speed may be found which will elicit barely perceptible compensatory movements of the head during rotation. But on suddenly stopping the rotation the animal will exhibit very marked compensatory movements. With the eyes open the effects are just the reverse. Two animals, one with the eyes open and the other with the eyes closed, may be placed on the same turning table at the same time, and these differences in deportment noted under exactly the same conditions of speed of rotation and suddenness of stopping. If the visual field is rotated at the same speed as the animal, the effects with the eyes open are the same as with the eyes closed. If an endless roll of paper with wide vertical lines marked

on it is rotated about the animal, there are compensatory movements of the head during the movements of the paper, but none after the paper has ceased to move.

The fact that the effect of rotation may persist in animals—frog (Ewald), turtle (Trendelenburg and Kühn) after bilateral lesions of the vestibule when the eyes are open but not when the eyes are closed had been known for some time previously, and the neglect of precautionary measures has led to some incorrect statements. The fact that, in Phrynosoma, the most marked compensatory movements of the head appear after rotation has ceased when the eyes are closed seems to dispose effectively of Schäfer's (52) analogy of the loosely jointed wooden head and his view that the compensatory movements of the head during rotation arise from the inertia of the head itself. Gruenberg (53) had concluded from experiments on the frog that the "spin" was the only constant element in the excitation of the vestibule during rotation, and Maxwell (54) showed on Phrynosoma that the torsion effect was the essential element. The two names appear to indicate exactly the same thing.

Trendelenburg and Kühn found that, after bilateral lesions of the vestibule, the common lizard, Lacerta agilis, showed no abnormal position of the head when at rest. From time to time, however, swaying of the head from side to side would appear. These movements were especially noticeable after the animal had been making rather vigorous movements of the body and had come to rest. The animals had great difficulty in catching the meal worms on which they were fed, the head swaying about so much that it was largely a matter of chance when a worm was caught.

Henri (55) considered it of interest from the theoretical point of view to investigate the effects of vestibular lesions in serpents because of their peculiar method of progression. The effects of vestibular lesions in the adder are manifested in various ways. There is a general feebleness and sluggishness of movement. The intact snake raises its head slightly above the ground in crawling, but, after operation, it rests or scrapes its lower jaw on the ground, and there is a tendency to turn to the injured side after unilateral operation. If held by the middle of the body, such an animal attempts to raise its head to reach the sustaining hand, but, in so doing, it turns its head around in a circle and rotates about the long axis of its body. The head is lower on the injured side when crawling or at rest. It may even rotate about its long axis in crawling. If placed on its back, it rights itself, turning always

to the injured side. Movements of the head may persist for some time after crawling has ceased. These observations were confirmed by Trendelenburg and Kühn. They found that the rolling movements of the body occur only when the snake is on a smooth surface, and not on a rough.

After bilateral operation, the position when at rest differs in no noticeable respect from the normal. But uncertainty is apparent as soon as the snake attempts to move. The head moves back and forth like a pendulum, with only momentary interruptions. If the snake is grasped by the anterior part of the body and shaken, the head moves aimlessly back and forth. In a normal animal the head moves along with the body. In swimming the head sways from side to side with the movements of the body instead of maintaining its median position, as in the normal specimen. Spiral bending and swimming occur at times. The back upward position in the water is very stable, even when the eyes are closed with collodion. Only when dropped from a height does the snake turn ventral side up in the water.

Most of the actual information derived from a experimental source as to the function of various parts of the vestibule and the mechanism of excitation has come from the study of the representatives of the three lower phyla of vertebrates. The rôle of the receptor in giving the animal control of the movements of the head is clear from a study of the experimental results. The difference in effect of unilateral or bilateral lesions upon various closely related forms with different methods of progression, but all of which are alike in possessing a central nervous system which does not show any very high degree of development, as compared with the mammalian type, and which vary from forms which spend their whole life in the water to those which enter the water only incidentally, are better shown here than in any other animal types used for experiment. One finds all variations from no receptor whose normal mechanism of excitation depends upon the aspect or change of aspect of the head in space, and no special effectors for correcting any variation of the head or body from the normal position, to a specialized receptor and a complete equipment of effectors. In between these extremes there are rudimentary or primitive effectors, or even their total absence. The eel and the serpent have no special effectors aside from the general musculature of the body. There are no paired appendages. But the presence of the specialized receptor enables the animal so to manipulate or control its general body musculature that all variations of the body and head from the normal position may be

remedied promptly and effectively. Similarly, Siredon may suffer the loss of all four limbs but, as long as the vestibular endings are intact, the animal suffers no loss of motor control in the water. One need go no further than the forms already described to find ample reason for doubting Ayers' (2) pessimism as to why the vestibular mechanism should have been evolved.

Passing from these lower vertebrates with the generalized nervous system to the birds and mammals, the nature of the problem changes somewhat. The increasing efficiency of the central nervous system as an integrating mechanism, and the increasing complexity, with a possible increase in its modalities, of a peripheral sensory mechanism shift the emphasis from the effects of the excitation or lesion of one peripheral sensory structure as we find it in lower vertebrates, to the ability of a more developed central integrating mechanism to compensate for and largely mask the effects of the loss of a single peripheral receptor. The development of the exteroceptors, and particularly of the distance receptors, in the land-living mammals and birds introduces another element. The free, powerful swimming fishes are dependent upon proprioceptors alone for the maintenance or control of the position of the body while in the water and not in contact with the bottom or other solid or motionless objects. There are few fixed points of reference in their environment of which they take cognizance through the exteroceptors, contact or distance. Probably there are few fixed points in the open ocean through or by which a whale orients itself, but with the other land-dwelling mammals, and particularly man, the case is different. There are few times in the life of an ordinary mammal on land when it is not in contact with the earth or some other fixed object. In the water or in the air, the case may be a little different, and the study of the effects of vestibular lesions in birds and mammals should be carried out under conditions as similar as possible to those under which the vestibular mechanism is of greatest usefulness in the lower vertebrates, that is, when an animal is prevented from coming in contact with fixed objects in the environment, or when, through elimination of vision, it is prevented from orienting itself through the visual exteroceptors.

It is to be presumed that the effects of vestibular lesions in lower vertebrates are more nearly objective than subjective. In the human, subjective effects appear, such as vertigo and the general group of sensations which have been included under the term sensation of rotation or of apparent movement. There is presumably an organic basis for

such sensations, but their analysis leads one into the central nervous system rather than to mere lesions of peripheral receptors. A fundamental principle in the interpretation of the effects of central nervous lesions in different animal forms enters in here,—the principle of the migration of function toward the anterior or cephalic portion of the central nervous axis (46).

Birds. The vestibule of birds has, from the time of Flourens to the present, held a central place in the study of its function. The work of Flourens on the experimental elimination of the internal ear marked the first stage in the experimental study of this receptor. The second stage began when Goltz (21) formulated his theory that the semicircular canals were sense organs for the perception of the position of the head in space. He proposed a hydrostatic theory of stimulation of the vestibule through changes in hydrostatic pressure of the fluid with the changing position of the head in space. The hydrostatic theory fell into disuse after the development of the dynamic theory of Mach, Breuer and Crum Brown. There is abundant evidence that the dynamic theory is applicable under many conditions of animal activity, but to discard totally the hydrostatic theory at present seems premature. We have only to remember that the change in the position of the eyes of a normal dogfish lasts as long as the head is held in the changed position, long after any inertia of the fluid in the vestibule has been overcome, to see one possible application of the hydrostatic theory. That it is not necessarily due to displacement of the otoliths is shown by the fact that the same displacement of the eye occurs after removal of the otoliths.

Ewald (56) called attention to the state of the vestibular problem at that time in the introduction to his first paper on the function of the vestibule in birds. Experiments up to that time had yielded, as they have up to the present, conflicting results. The effects of vestibular lesions in birds, up to that time, had been more severe and more permanent than the effects of similar lesions in fishes or mammals. The most reliable work on fishes has appeared since 1887, and the effects of vestibular lesions in birds have gained enormously in clearness, accuracy and fulness of detail from the work of Ewald himself. Better methods of operation have been devised in mammals, and the observations of the effects of lesions have been more carefully made since that time, but the differences in effect which Ewald noted are still more or less apparent. The immediate effects of operation are very similar in severity in all types of vertebrates which have come under my

observation, but the remote effects differ in intensity, and particularly under varying conditions. The effects of bilateral lesions in larval frogs are more severe than the effects of similar lesions in birds or mammals. The severity and permanency of the effects in Siredon are fully equal to those in birds, and more than equal to the effects observed in mammals under ordinary conditions. Ewald's statement, therefore, needs some revision in view of the greater number of facts now available on a greater range of animal forms.

Ewald stated three possibilities, one or more of which might account for this difference in the effect of vestibular lesions: *1*, There may be a difference in the topographical relations of the vestibule in different types of animals, so that contiguous structures may be damaged in different degrees in vestibular operations on various animals. For example, neighboring regions of the brain may be damaged more in birds, less in mammals, and not at all in fishes. It was not until Lange (57) showed that the effects of vestibular lesions in birds were not dependent in any degree upon injury to the cerebellum that this question was answered for birds. And no good experimenter need inflict any injury whatsoever upon the central nervous system of any animal in operating upon the vestibule. *2*, We may say that the vestibule has different functions, or at least different degrees of the same function, in widely separated groups of vertebrates. Fish may have a rudimentary development of the vestibular sense, mammals a somewhat better development, and birds the highest development of all. By way of comment on this possibility, it may be said that we have no index of the acuity of the vestibular endings in any vertebrate except man. It is possible, of course, that the acuity of the vestibular sense, to follow Ewald's terminology, may vary in different animal forms just as the acuity and sharpness of vision or the acuity of smell may vary, even in different individuals of the same species. *3*, We may say that the vestibule has the same function in different animal forms, and that, following its destruction, the same functional defects appear in all of them; but these defects may be more or less, possibly completely, obscured by the static conditions under which the animal lives. Under these static conditions are included the general structure of the body, the length of limbs, the length of the neck, the number and size of the points of support, the topography and size of the supporting surface, in relation to the form of the body and the medium in which the animal lives. These considerations are important. As I have mentioned above, the animals living on the land are, under all ordinary circum-

stances, in contact with a solid surface, that of the earth itself, only occasionally, depending largely upon habit, going into the water or into the air. Birds go into an even more unstable medium than water,—the air. It seems to me that we should now add at least one more consideration, *4*, that of the degree of development of the exteroceptive sense organs, particularly the distance receptors, and the degree of development of the central nervous system itself.

In order to test out these various possibilities, Ewald made a series of experiments on various representatives of a single phylum and chose birds. In this phylum, if one does not choose genera too remote from each other, the topography of the vestibule is too similar to permit of many differences in effect arising from varying degrees of injury to contiguous structures, and one would think still less of a difference in function of the vestibule in different families of the same phylum. On the other hand, the static conditions in different families and genera of birds vary greatly according to whether they run, jump, fly or swim. The mode of station at rest also varies, as some lie, sit, stand on two legs or on one. Such a study should bring out the extent to which the functional disturbances following lesions of the vestibule are dependent upon the static conditions of the birds chosen for experiment. Ewald's results are given in the accompanying table.

Ewald emphasizes the fact that the difficulty in flying is more marked in birds whose wing movements are more rapid than in those birds whose wing movements are slower. The swallow had the most highly developed powers of flight of any of the forms used for experiment, and the disturbances were greatest in this bird. He draws the general conclusion that when one makes the same destructive lesion of the vestibule in each of a series of different forms of birds, the resulting disturbances of movement are greater the more difficult it is for the bird to maintain its equilibrium normally in one form of progression, and the greater or more rapid the degree of muscular coördination required for its successful execution.

Experimental work has been carried out in birds, and particularly in pigeons, in much greater detail. In general, there is torsion of the head to the injured side, sometimes leaning of the body to that side, inequalities of wing movements, the movements being less extensive and of less force on the injured side, and a loss of general muscular tonus on one side, when the lesion is unilateral. Rotation is attended by head movements, head nystagmus, as Breuer calls it, and ocular nystagmus, in normal birds. The reactions to rotation are lost after bilateral

vestibular lesions when the eyes are covered. There is also a great disturbance in the sense of position of the head, and Ewald argues for a permanent loss of tonus of the neck muscles.

Bornhardt (58) applied ice to the left posterior vertical canal of a pigeon and observed rapid movements of the eyelids, the eyes being closed; when the pigeon attempted to move, there were rather feeble backward movements of the head and traces of circus motion. Continued cooling of both posterior vertical canals increased the backward movements of the head and the tendency to fall backward. Pendulum

TABLE 1

DISTURBANCE	FLYING	JUMPING	HOPPING	WALKING	SWIMMING	STANDING
Very marked	Swallow					
Marked	Sparrow	Raven				
Moderate	Pigeon Raven	Sparrow	Raven Sparrow			
Slight	Hen			Raven Pigeon Hen		
Transitory	Goose			Goose	Goose	Raven Hen Sparrow Pigeon Goose

movements of the head, occasionally passing over into circus movements of the body, also appeared. All effects disappeared in fifteen minutes after cooling was intermitted. The application of a hot rod to the left horizontal canal of a pigeon caused movement of the head to the right and closure of the eyelids. When the eyelids were opened there was strong deviation of the eyes to the right, with quick jerks to the left. Burning the right horizontal canal of the same bird caused movements of the head to the left, but less marked than when it had before turned to the right, and it soon returned to the midline.

Considerable work has been done on mechanical stimulation of various separate canals in the pigeon. Ewald (38), by means of his pneumatic hammer, set up pressure in a canal which was transmitted to its ampulla. There was, in the case of the horizontal canal, a movement of the head

to the opposite side in the plane of the canal. There is usually a return to the normal position immediately afterward. When the pressure is relieved, there is a movement of the head toward the side stimulated, but less marked than when the pressure was increased. In the case of the superior (vertical) canals, the movement following the relief of pressure is more marked than the movement following the increase of pressure. There is also movement of both eyes, the direction of the movement being the same in the pigeon as in the dogfish.

It should be pointed out that Maxwell's result on the transmission of pressure from the utricle to the ampullae of the various canals is not in any way inconsistent with Ewald's results. The facts seem to indicate that, wherever the pressure may arise, whether in the canals or in the utricle, its transmission to the ampullae is sufficient to excite the nerve endings within them. This is the important thing to be remembered in formulating any hypothesis of the normal mechanism of excitation of the ampullae.

Breuer (31) has repeated, on pigeons, Gaglio's (29) experiments on the application of cocaine to the vestibule. There is an agreement that simple anesthesia of the vestibule is attended by the same effects as its anatomical destruction. Breuer, however, disagrees with Gaglio in some matters of detail.

Borries (59), basing his conclusions partly upon experimental results in pigeons and partly upon clinical observations, thinks that the changes in the reaction to irrigation of the ears with water colder or warmer than the body,—the caloric nystagmus of the clinician,—with the changes in the position of the head are dependent upon the otoliths. I am unable to follow the reasoning involved in arriving at such a conclusion. While it has been shown by various experiments that we must probably attach more importance to the otoliths than we have heretofore, it has not yet been shown that the ampullae of the vestibule are without any functional importance. It seems much more likely that we must regard both parts of the vestibule as functioning together to bring about a common reaction.

Mammals. Although the first experimental observations on the effects of excitation of the vestibule were made by Darwin and Purkinje, perhaps even by Theophrastus, on the human subject, the greatest knowledge of the functions and manner of excitation of the vestibule has not been derived from observations upon the human or even upon mammals. As has been indicated, the nature of the problem changes somewhat when one reaches the birds and particularly the mammals.

Vertigo, with which Purkinje dealt, is a subjective thing and not wholly objective. Its consideration goes far beyond the mere function of the vestibule and leads to a problem of extreme complexity in the central nervous system itself. Purkinje's results have been so well presented elsewhere (60) that their consideration here is superfluous, and the problems of the central nervous system are much too complex to enter upon here. Raines (61) has given a specific instance of the phenomena of vertigo appearing under certain conditions in aviators.

The ocular nystagmus, mentioned in birds, is a prominent feature of the effects of rotation in mammals. The detailed description of all forms of ocular nystagmus is given by Coppez (62). The typical form of vestibular nystagmus, as observed in man and the higher mammals, is not elicited by lesions of any other nervous mechanism, so far as my observation or knowledge goes, and it does not appear in typical form in lower vertebrates. Its consideration becomes not so much a question of vestibular function as a problem of the connections of the vestibular and oculomotor nerves within the central nervous system. As Eckhard (63) states, when it is certain that no injury to the medulla oblongata occurs, there is no ocular nystagmus following lesions of the cerebellum. Our original statement that complete removal of the cerebellum in the dog does not prevent the appearance of vestibular nystagmus has now been confirmed by Magnus for other mammals.

Hitzig (64) showed that exactly the same phenomena of vertigo could be produced by electrical stimulation of the vestibule as result from rotation of an animal or man. The clinical application of the electrical method of stimulation of the vestibule has been considered by Babinski (65) and others.

All mammals, except man, show the torsion of the head to the injured side after unilateral vestibular lesions, with rolling movements to that side during the first few days. The torsion of the head is permanent, but the rolling movements and the nystagmus are transitory. The same effects are often seen accompanying abscesses of the inner ear in white mice and rats (66), guinea pigs and rabbits. I have never seen a case of an abscess of the internal ear in cats or dogs. Walking or running in a circle to the injured side is also a transitory effect of a unilateral vestibular lesion.

After bilateral operation there is a slow swaying of the head from side to side, especially in cats, while dogs remain flat on the floor for some days afterward, refusing to walk or even stand. The decerebrate animal will stand, even after removal of both vestibules (67). Walking

or running in a straight line soon becomes possible, and dogs or cats exhibit no noticeable defects of locomotion when on the ground. When the eyes are covered, the dog has difficulty in walking in a straight line, turning from side to side in an irregular way. Swimming with eyes open is a matter of great difficulty or even impossible in such an animal. It may swim on its side or back or turn downward toward the bottom of the pool. After unilateral operation a cat or dog will jump over the side of the cage or from a considerable height to the ground without falling or exhibiting any defects of movement. But a dog will not jump from even a moderate height to the floor without falling in a heap after bilateral operation. This observation was made by Schiff (68), and we have many times confirmed it. After one or two experiences, a dog will look over the edge of the table and whimper when food is held some distance from him, but he may refuse to jump to the floor in order to get it. Under conditions where the animal is deprived of the use of its proprioceptors and exteroceptors with the exception of sight, as in jumping or swimming, the effects of vestibular operations may be shown in dogs months afterward.

The deviation of the eyes is permanent in lower vertebrates following unilateral vestibular lesions, but it is merely transitory in higher forms. It has been found, also, that the nystagmus following rotation may be decreased or even abolished by repeated rotation of an animal or man on successive days (69), (70), (71). And with reduction of nystagmus there is a reduction in the degree of vertigo experienced in men. This does not seem to indicate any particular difference in the function of the vestibule of higher forms as compared with the lower, but to indicate that there is a considerable difference in the central nervous relations of the vestibular and oculomotor mechanism in higher forms. The problem again becomes one of the organization of the central system and its changes in phylogenetic development. And no place outside of the vestibule can one find any part of a proprioceptive mechanism which is circumscribed in location and which is capable of complete anatomical removal with so little damage to any contiguous nervous structures. For this reason as well as because of the very definite motor and postural disturbances following anatomical lesions the vestibular nerve endings offer a unique opportunity for the analysis of the central relationships of an extremely important proprioceptor. The problem is as yet unsolved.

Dodge (72) has made the only determinations of the threshold of stimulation of the vestibular endings known to me. The threshold

lies between 1° and 2° per second for sine curve acceleration beginning at zero. During actual rotation the threshold seems to be higher, as a change of 6° a second seems necessary before the subject notices any change in the rate of rotation.

Aside from the ordinary results of rotation, some other facts of interest have been noted in connection with the mammalian vestibule. Magnus and de Kleijn (73) showed that when a cat's head was lowered, the vestibules being intact, the fore legs were flexed and the hind limbs extended; when the head was raised, the fore limbs were extended and the hind limbs flexed. The numerous other papers of these authors are given in Griffith's (11) bibliography.

Wilson (74) has shown that high explosives may so affect the cochlear portion of the ear that hearing is impossible, but the vestibule may remain relatively uninjured. The history of the separation of the auditory and vestibular functions of the internal ear is given by Gellé (75). Another extremely important series of observations is that of Holmes (76) on the effect of gunshot injuries of the cerebellum. As Holmes points out, the effects of gunshot injuries in the human are more nearly comparable with the experimental results in animals than are the effects of ordinary pathological lesions.

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ADDENDUM

The two following important publications were received too late for comment in the text.

Maxwell, S. S. Labyrinth and equilibrium. Philadelphia and London, 1923.
Muskens, L. J. J. Brain, 1922–23, xlv, 454.

ANTI-ANAPHYLAXIS AND DESENSITIZATION

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The recent reviews by Arthurs (1), Bordet (2), Coca (3), Dale (4), Wells (5), Zinsser (6) and particularly the extensive articles by Doerr (7) have presented the subject of anaphylaxis in so many of its phases and so satisfactorily that it seems unnecessary at this time, and is obviously impossible in the space devoted to this article, to repeat what has already been so thoroughly discussed in these papers, most of which are readily accessible. As the outline by Wells that appeared in the PHYSIOLOGICAL REVIEWS for January, 1921, gives in an admirable way the general knowledge of anaphylaxis as it has been developed experimentally, therefore an attempt will be made in this review only to elaborate one or two phases of the subject that have not been so exhaustively discussed in these articles.

The recognition of states of sensitization in the human being that simulate or are analogous to the anaphylactic state in the animal has, for some years, attracted attention, and a considerable amount of work has been done in an endeavor to determine what diseases owe their origin to this condition of hypersensitiveness. Through these studies it has been well established that in many patients hay fever, asthma, acute intestinal disturbances occurring particularly in children, various forms of skin affections, such as eczema, urticaria and different types of dermatitis and occasionally angioneurotic edema, depend upon the fact that the individual possesses an abnormal hypersensitiveness toward some substance, often, but not invariably, containing foreign proteins. The most common of these are the pollens of plants, the dander and hair of animals, the feathers of birds, food substances, and even drugs and chemicals. It seems clearly proven now that there are direct relationships between hay fever and the inhalation of certain varieties of pollen, between the perennial forms of rhinitis and asthma and the inhalation of the dander of animals, the dust from feathers, the powder of roots, such as orris, or the ingestion of foods such as eggs, milk and cereal. A direct association has further been established between the appearance in certain individuals of eczema, urticaria,

different forms of dermatitis and angioneurotic edema and the contact or ingestion of many of the substances already mentioned or even of chemicals. In an attempt to relieve the individual of the affection from which he has been suffering, methods have been employed to reduce or to abolish the state of hypersensitiveness which is known to form the basis of these reactions, and it is particularly with the subject of anti-anaphylaxis or desensitization that this review will deal.

The original observations upon which all subsequent efforts to bring about suppression of the state of anaphylaxis by special methods have been based were made by Besredka and Steinhart (8), confirmed almost immediately by Otto, Rosenau and Anderson and Gay and Southard, and developed experimentally especially by Besredka and Weil.

With the object of finding some method that might be applicable in preventing anaphylactic shock and serum disease arising in man after the use of horse serum for therapeutic purposes, Besredka (9) experimented with a great number of substances, which, it was hoped, might counteract the effect of the hypothetical poison that was at this time supposed to induce the anaphylactic shock. Among other methods he tried the effect which heat had on the horse serum that was employed for the second or intoxicating dose of protein injected into the sensitized guinea pig. This disclosed the fact that heat impaired materially the activity of serum employed for the second injection. Horse serum, diluted in the proportion of 1 to 4 with distilled water to prevent coagulation, he found could be heated to 76°C. for 20 minutes without materially affecting its activity. Kept at a temperature of 89°C. for 20 minutes, some decrease in activity was observed. This impairment was more evident when the diluted serum was kept at 95°C. for the same length of time, and at a temperature of 100°C. for 20 minutes the activity of the serum was completely abolished. Provided the horse serum was heated, many times the fatal dose could be injected intravenously in highly sensitized guinea pigs without causing untoward symptoms. Besredka further observed that though the injection of heated serum might be harmless, it possessed the power of protecting the guinea for some time against injections of unheated serum, which, in themselves, were surely fatal. Further experiments demonstrated that the same effect could be obtained with the specific unheated serum when this was injected subcutaneously, intraperitoneally, intrathecally, or intravenously in amounts considerably below the minimal lethal dose. Sensitized guinea pigs could thus be protected against several times the lethal dose of horse serum by a single injection that was

200 to 500 times below the lethal dose. This refractory phase which Besredka first called anti-anaphylaxis was later designated by Weil, and indeed Besredka himself, as desensitization, a term which describes much more appropriately than anti-anaphylaxis this particular condition. It will therefore be referred to in this article as desensitization.

Thomsen (10) has stated very clearly the theories that may be offered to explain desensitization. He suggests that this may occur in at least three ways:

I. By the destruction or exhaustion of the antibody (occasioned by the preliminary injection).

II. By the interference with the reaction between antigen and antibody.

III. By the insusceptibility or diminished activity of the animal toward the shock-producing factor, which is an hypothetical and indefinable substance.

It may be seen that these explanations assume first that an antibody is formed toward the specific protein which is introduced parenterally; and secondly, that the symptoms of anaphylactic shock are in some manner associated with the union of the specific antigen and antibody. It is not possible in the present article to bring forward all the evidence in support of this view, but it is sufficient to say that though investigators have differed in their opinion as to the situation and the manner of the union between antigen and antibody, and though the intermediate steps between this union and the actual evidences of anaphylactic shock are still very obscure, still there is general agreement that the symptoms, which result from the injection of a specific protein in a sensitized animal are, in some way, dependent upon the interaction of antigen and antibody.

To explain the protective effect of a single sublethal dose of specific protein against a lethal dose in a sensitized guinea pig, Besredka advanced the hypothesis that the protein given in the preliminary injection, united with the antibodies and by doing so reduced their potency or combining power. This resulted in a condition which necessitated the injection of much greater amounts of antigen in subsequent injections in order to bring about an explosive reaction with death. His experiments seemed to show, moreover, that it was possible to increase, almost to an indefinite point, the tolerance of sensitized guinea pigs toward the specific protein by repeating, at short intervals and in increasing amounts, injections of the specific protein. Thus a sensitized guinea pig, for which an intravenous dose of 0.05 cc. of serum would be fatal

was given 0.025 cc. of serum intravenously without harm; 5 minutes later 0.10 cc. without serious symptoms; 2 minutes later 0.25 cc. without symptoms, and 2 minutes later 1.0 cc. could be administered, twenty times the lethal dose, without harm. This method of desensitization could be employed in passively sensitized animals as well as in actively sensitized animals. The preliminary injections were efficacious when administered by vein, intracerebrally, intraperitoneally or subcutaneously. Larger doses were necessary for desensitization when the injections were made intraperitoneally or subcutaneously, and required a much longer time to take effect than when administered intravenously. The fact that a rapid union of antigen and antibody is necessary for the production of the explosive reaction that characterizes anaphylactic shock, led Friedberger and Mita (11) to employ a method of desensitization which varied in technique from that employed by Besredka. They showed that when horse serum highly diluted with salt solution was infused at an extremely slow rate into sensitized guinea pigs, desensitization could eventually be established, and that guinea pigs treated in this manner were refractory to large doses of horse serum.

In general these observations have been confirmed by Friedberger and Mita, Weil (12) and many subsequent investigators; but not infrequently such irregularities occur in the results that have been obtained during the course of desensitization, that the correctness of Besredka's view has been called in question. Thomsen, who has experimented most carefully on this subject, emphasizes the fact that the rate and degree of sensitization varies considerably in different groups of guinea pigs, is influenced by the age of the animal and is affected materially by the size of the sensitizing dose. It is well known that small doses of serum sensitize guinea pigs more rapidly than large doses. In Thomsen's experiments an injection of 0.004 cc. of horse serum, in one group of guinea pigs, resulted in increasing sensitiveness up to the 25th day; after this time the degree of sensitization gradually diminished, but was still present 285 days after the original injection. When the sensitizing dose was larger, 0.1 cc., the height of sensitization was not reached until the 62nd day after injection; but, on the other hand, persisted for at least 365 days. He further confirmed Friedberger and Simmel (13) in the view that on the one hand very young guinea pigs and on the other old guinea pigs are much more resistant both to active and passive sensitization than are guinea pigs which weigh from 200 to 600 grams. It is obviously of great importance to keep these facts in mind when considering the results of any method of desensitization,

for Thomsen shows quite clearly in his experiments, that it is much more difficult to desensitize guinea pigs that are highly sensitized, than those whose sensitization is of only moderate degree. With high grades of sensitization one-half the m.l.d. of horse serum injected intravenously increased the resistance of the guinea pig very slightly, was perceptible in 2½ hours and persisted for 8 days; whereas with moderate grades of sensitization a single intravenous injection of one-half the m.l.d. increased the resistance of the guinea pig 30 times, was partially effective in 20 minutes, completely effective in 2½ hours and persisted 8 days. The same quantitative relation between the degree of sensitization and the relative difficulty of desensitization held when the guinea pigs were sensitized passively, for guinea pigs, made passively sensitive by the injection of small amounts of antihorse rabbit serum, could be much more readily desensitized to horse serum than those injected with large quantities. Thomsen's experiments seem to show that there is a close relationship between the amounts of antibody in the sensitized guinea pig and the relative difficulty of desensitization, the presence of large amounts of antibody rendering desensitization difficult; and he concludes that during the process of desensitization antibody disappears.

It seems quite clear also from the work of Dale and his co-workers (14), Weil (15) and others, that it is the tissue cells which are exhausted of their antibody during this process of desensitization. Dale, who has developed so extensively the use of the cornu of the uterus in experiments upon anaphylaxis, showed that the entire process of desensitization could be carried out in vitro; for, if a guinea pig is sensitized to two different proteins, the addition of one specific protein to the Ringer's solution, in which the uterine segment is suspended, renders the uterus insensitive to subsequent application of this specific protein, but leaves the reactivity of the uterus unimpaired toward the second protein to which the guinea pig was sensitive. The experiments of Dale and his co-workers are of great importance in demonstrating the fact that the mechanism of specific desensitization affects the tissue cells, in both actively and passively sensitized guinea pigs, and further throw light upon the condition of the cells during their phase of desensitization. One may ask whether the cell during this period is restored to a condition which approximates normal, and is devoid of all substances that might react either with antigen or antibody. Weil (16) has made some important contributions to this subject, for he has shown that when a guinea pig, which has been sensitized to horse serum, is desensitized by

repeated injections of horse serum, the animal may, during this period of desensitization; be passively sensitized to horse serum with the same facility as a control normal guinea pig. These experiments would indicate that, during the phase of desensitization, not only is the antibody completely dispensed with, but the cells return to a state which so nearly approximates normal that they are susceptible of passive sensitization to the same protein.

Such experiments have been carried out not only in vivo but in vitro, as Dale has demonstrated by employing the strips of uterine muscle. In Dale's (17) experiments the uterus of a guinea pig, passively sensitized to horse serum, was removed, suspended in Ringer's solution and treated with horse serum. The reaction which followed the first application could not be obtained again by applications made some minutes later. This indicated that the uterine muscle had been desensitized. After thorough washing, the muscle was soaked for $2\frac{1}{2}$ hours in 10 per cent dilution of serum from guinea pigs anaphylactic to horse serum, and then washed in numerous changes of Ringer's solution. The response to a further addition of horse serum showed that passive sensitiveness had again been conferred upon the muscle in vitro, and could again be removed by an effective dose of antigen, since further additions of horse serum had no effect.

It is to be noted that, during the process of specific desensitization, the affinity or receptivity of the antibody for the antigen gradually diminishes; though in the partially desensitized animal such an affinity may still persist. In the partially desensitized state, however, much larger doses of antigen are required to produce a reaction than before desensitization has been started. As Weil (18) has pointed out, the quantitative relationships between the supposed union of antigen and antibody differ from those observed between precipitin and precipitinogen, and resemble more closely the phenomena encountered during toxin antitoxin neutralization when small quantities of antitoxin are added to toxin.

These experiments, which have been purposely set forth in some detail, all lead to the conclusion that specific desensitization of both actively and passively sensitized guinea pigs is brought about by the neutralization or exhaustion of the specific antibodies. This conception of the process has been adopted by most authorities, and by many the view is accepted that the process of desensitization takes place within the cells of the body.

Before considering the application of these methods of specific desensitization to therapeutics, it is necessary to call attention to another form of insusceptibility to anaphylactic shock, that was observed by Rosenau and Anderson to follow the repeated injection, at short intervals, of foreign protein in animals. Guinea pigs treated by this method are found to be highly insusceptible to anaphylactic shock. At the same time they contain specific antibodies circulating free in the blood, so that their serum, when injected into a normal guinea pig, is capable of sensitizing this normal animal passively to the specific protein. In rabbits treated by this manner the serum not only contains large amounts of antibody or anaphylactin, but is very rich in specific precipitins; and, as Doerr and Russ (19) have shown, there is a very close quantitative relationship between the precipitin content and the anaphylactin content of the serum of these immunized rabbits. The protection which these animals possess against injections of antigen seems to reside in the presence of these circulating antibodies, which unite with the antigen and prevent it from injuring the cells of the body. When these antibodies are removed from the circulation, as has been shown by Weil (20), the guinea pig becomes highly susceptible to injections of antigen. Likewise, when the organs are deprived of this protection they show in vitro the reactions that are characteristic of the highly sensitized animals. The experiments of Dale and of Manwaring and Kusama (21) show that the organs removed from immunized guinea pigs, and washed free from all circulating antibodies, react in the same manner to the specific antigen as the organs from highly sensitized guinea pigs, and these experiments add convincing evidence for the conclusion that the protection of these animals resides in the presence of free antibody in the circulating blood.

Specific desensitization of human beings. The original investigations of Pirquet and Schick (22) on serum disease showed that second injections of horse serum, made at a considerable interval after the first injection, might give rise to an immediate reaction somewhat like the usual forms of serum disease following the first injection but often of rapid onset and very severe in nature. The analogy to anaphylactic shock in the guinea pig or rabbit is striking and it has usually been considered that the fundamental process of sensitization by the artificial injection of foreign proteins is the same in the human being as in animals. This supposition has, however, recently been called in question by Coca (23), who upholds the view that serum disease is only one form of the so-called "hypersensitiveness." and is dependent upon a

state of reactivity of the tissues of the individual which endows them with a special hypersensitiveness toward the proteins of horse serum, a condition that he terms "allergy" and that he classifies with "drug allergy," "food allergy" and "pollen allergy." All of these "allergies" he believes are fundamentally different from experimental anaphylaxis in the animal inasmuch as he considers that the reactions take place independently of a specific antibody antigen reaction and are inheritable. Most of the arguments which he elaborates against the original conception of Pirquet and Schick, that serum disease is produced by a toxic substance that results from the interaction of newly formed antibody with persisting antigen, are based on such factors as the following: *a*, The irregularities in the length of incubation period; *b*, the conflicting observations upon the results following second injections, the occurrence of immediate reactions, and the difficulties of desensitizing the patient who is "allergic" to horse serum; *c*, the irregularities in the occurrence and relationship of such circulating antibodies as precipitin and anaphylactic antibody to the serum sickness, together with the relationship which the appearance of these antibodies bear to the onset, duration and termination of serum disease; and finally *d*, what he considers to be a remarkable similarity between the phenomena of "drug allergy" and "serum allergy." Before it is possible to discuss intelligently the mechanism of desensitization in the human being, it is important to see in what manner and how far analogies can be drawn between the anaphylactic states in animals and artificial sensitization in human beings.

In spite of the objections which Coca has raised to the view that an antibody antigen reaction is responsible for serum disease and the hypersensitiveness, that is known to develop in the human being after the artificial injection of foreign proteins, the evidence which he brings forward is scarcely sufficient to warrant, at the present time, the separation of serum disease and artificial sensitization in the human being from anaphylaxis as it occurs in animals. When the facts are reviewed there is indeed much to uphold the idea that the two processes are fundamentally the same.

It has long been recognized that different species vary in the readiness with which they may be sensitized to foreign proteins. Guinea pigs may be sensitized with extremely small doses of proteins, dogs and cats are less readily sensitized, rabbits are much more difficult to sensitize, monkeys are highly refractory (24), while rats seem to be entirely refractory (25), (26). Observations upon the effect of injections of horse

serum in man indicate that sensitization can only be accomplished with considerable difficulty, when compared with such animals as the guinea pig. According to collected statistics (27), (28), (29), it requires considerable quantities of horse serum to sensitize man and the incidence of serum disease as well as the subsequent sensitization varies with the dose of serum administered and increases in proportion to the amount. After the injection of 10 cc. of horse serum, only about 10 per cent of patients present symptoms of serum disease, whereas injections of 90 to 100 cc. of horse serum result in serum disease of varying degrees of severity in about 90 per cent of the cases. The variations in the incidence and incubation period of serum disease probably depend upon several factors, but one factor, which is evidently important, is the amount of serum that is administered.

Another factor which has been emphasized by Mackenzie and Leake (30) is the individual variation that is much more striking in the human race than in most species of animals. The observations of Coca, Deibert and Menger (31) upon the incidence of serum disease in the North American Indian demonstrates clearly that members of this race are much less likely to have serum disease, after the administration of 100 cc. of horse serum intravenously, than members of the white race. They give the percentage incidence as 46 per cent in 26 Indians as against 92.4 per cent in 52 whites.

When compared with the results obtained in many animals, single or even multiple doses of horse serum render human beings relatively slightly sensitive to subsequent injections of horse serum; but the observations of Pirquet and Schick, Goodall (32) and Klimenko (33) show that serum disease occurs with greater frequency after second injections of small doses of horse serum than after the first dose. Moreover, when the second injection is made after a considerable time interval, the reaction to the serum is likely to appear within a few minutes to 24 hours following the injection and is frequently violent and of short duration. Goodall states that in 1260 cases receiving a first injection of diphtheria antitoxin 464 or 36.8 per cent developed serum disease; whereas in 203 cases, receiving a second injection from 2 weeks to 13 weeks after the first, 129 or 63.5 per cent reacted. Moreover, the incubation period following the first injection varied from 6 to 15 days in 90 per cent of the cases, whereas in the reinjected cases the serum disease made its appearance within 48 hours in 50 per cent. Furthermore, the first dose of serum may sensitize without in itself producing the visible reaction—namely, serum disease. From the

statistics published by Goodall it seems probable that individuals suffering from an attack of serum disease caused by the first injection are especially prone to react to the second injection. Of 188 patients, half of whom had not had serum disease and half of whom had had serum disease following the first injection of diphtheria antitoxin, 20.4 per cent of the former reacted to a second injection, and 70.77 per cent of the latter. Though all the collected statistics do not agree in detail with those of Goodall, still those of Klimenko and others show a much higher proportion of reactions following the second dose of serum than occur after the first; while the skin reaction, caused by the intracutaneous injection of horse serum, that may be obtained shortly after the occurrence of serum disease, and, which may appear even after a dose of horse serum which has not called forth a generalized reaction, is known to persist for many years. Employed first by Moss (34) as a test to detect sensitization, the skin reaction has been used extensively to determine the presence and degree of sensitization of patients who, for therapeutic purposes, require an administration of antisera months or years after a previous injection. All of the observations point to the fact that the primary injection of horse serum may in itself alter the cells of the body in such a manner that they respond to a second injection as do sensitized animals, with greater rapidity and in a more explosive manner. Inasmuch as serum disease, which may be looked upon as the evidence of a primary reaction, shows considerable irregularity in its occurrence, it is not surprising that the reactions appearing after the second injection are also somewhat irregular in their occurrence, in their severity, in their incubation period and in their duration. Much depends upon the dosage, the method of administration and the interval of time that elapses between the first and second doses. These factors are equally important in determining the effect which is obtained with the second dose of horse serum in sensitized animals.[1]

[1] It is possible, as Taniguchi (Journ. Path. and Bacteriol., 1922, xxv, 77) has recently suggested, that some of the immediate reactions which have been observed in human beings, with the first injection of horse serum, may be dependent upon the presence of heterophile antibodies of Forssman (Biochem. Zeitschr., 1911, xxxvii, 78; Forssman and Hintze, Biochem. Zeitschr., 1912, xliv, 336). Taniguchi points out that heterophile antibody is frequently abundant in human serum, and that horse serum often contains heterophile antigen. The introduction, therefore, of horse serum into the circulation might afford an opportunity for the union of the heterophile antigen injected with the heterophile antibody in human serum, and give rise to a reaction which is indistinguishable from anaphylactic shock.

Coca has questioned the correctness of the conclusions which have been based on the demonstration of antibodies in the serum and which have been taken by some to indicate that the fundamental principles of sensitization are the same in man and animals. It has been repeatedly demonstrated that man is capable of producing such antibodies toward horse serum as precipitin and anaphylactic antibody, but it is difficult to state that the appearance of these antibodies in the blood serum bears a direct relationship to the onset, the duration or the subsidence of serum disease. Hamburger and Moro (35) believed originally that there was a reaction between precipitin and precipitinogen in the circulation, and that this was the actual cause of serum disease. There seems, however, to be no foundation for this view. Several observers, finding considerable irregularities between the occurrence of serum disease and the appearance of precipitins in the circulation, have concluded that the two processes bear no especial relationship to each other (36), (37), (38); while others (Weil) have thought there was a relationship and, finding precipitin in high concentration in the serum toward the end of serum disease, have advanced the idea that the production of these antibodies in excess is associated with the termination of serum disease, and may be regarded as an effort on the part of the body to dispense with the antigen (39), (30). Some recent experiments of Mackenzie and Fruhbauer (40) have cast doubt upon this latter idea for they have observed that repeated injections of large amounts of antihorse rabbit serum into the veins of rabbits that have been previously treated with horse serum have no effect upon the rapidity of disappearance of horse serum from the circulation of the rabbit. One possible error in drawing conclusions from observations upon precipitin formation, lies in the fact that precipitins and anaphylactic antibody have often been considered as identical. It is not, however, justifiable to apply this conclusion universally, for it has been shown that though the white rat forms specific precipitins for horse serum this animal cannot be sensitized to this protein.

One may conclude, however, that the human being is capable of forming specific antibodies to horse serum such as precipitins and anaphylactic antibody; and that the mechanism of the production of these antibodies conforms to the same general laws as it does in such animals as the rabbit, for though the time of their appearance in the circulation after the first dose of horse serum may differ in the two species, this in both species may be greatly shortened after the second injection of antigen (41).

It is therefore impossible to lose sight of the fact that the human being is capable of reacting to horse serum by the production of specific antibodies toward this foreign protein, and that following injections of horse serum the cells acquire the property of reacting more promptly and with greater vigor to second injections; and it is difficult to escape the original view of Pirquet, which most authors, including Dale and Doerr in their most recent reviews uphold, that serum disease itself is dependent upon an antigen-antibody reaction, and that the subsequent sensitization is due to the presence of antibodies in the tissue cells.

If the conclusion is correct that the injection of horse serum in man produces a state of sensitization which is comparable to that in the guinea pig or other animals, and that is dependent upon the formation in the cells of the individual of specific antibodies toward the protein injected, it should be possible to reproduce in man, as is possible in specifically sensitized animals, the states of specific desensitization and of immunity. To this end the method devised by Besredka has been repeatedly employed with varying degrees of success. In dealing with the sensitized patient it is impossible to determine the minimum dose of serum which will cause symptoms when administered either subcutaneously or intravenously; and it is, therefore, impossible to gauge the doses with any approximation to accuracy. Inasmuch as the second injection is rarely dangerous, unless the serum is given in large amounts intravenously or intraspinally, it is not often that attempts are made to desensitize the patient with accuracy or care. There is considerable evidence to show that the experiments of Otto and Hoefer (42) are inapplicable, and that single doses of horse serum will not desensitize highly sensitized individuals against intravenous or intraspinous injections of horse serum (43), (44), (45), (46). Instances are on record, however (47), in which patients previously injected with horse serum, who were found to be so highly sensitive to this protein that the injection subcutaneously of such small amounts of horse serum as 0.4 cc. called forth the immediate generalized symptoms, could be rendered insensitive to an injection of 8.0 cc. of horse serum intravenously, by giving first 0.025 cc. of horse serum subcutaneously and repeating in increasing amounts the dose of serum; first subcutaneously, and then intravenously. During this process of desensitization mild generalized reactions were observed after 3 of 15 injections. Though few cases that have been carefully studied are on record, it appears to be possible to carry out specific desensitization of man in much the same manner, though not as effectively, as in animals. It is obvious that

absolute desensitization is difficult to accomplish, and that during the process of desensitization, general reactions may follow increases in the dose, especially when this is given intravenously. But the same phenomenon is observed in the desensitization of specifically sensitized guinea pigs and has been commented upon particularly by Weil. There does not appear to be any reason, therefore, to consider that specific desensitization under these conditions is essentially different in man and animals.

There seems to be little accurate information concerning the possible immune state in man. Repeated primary injections of horse serum, given at short intervals, have no effect upon the incidence or the incubation period of serum sickness itself, for it cannot be prevented by this method. There does, however, seem to be a period following serum disease, in which the patient shows considerable resistance to second injections of the same serum. Goodall found that of 45 patients, reinjected within 5 weeks of the first injection, only 37.7 per cent showed serum disease while of 47 reinjected after the 27th week 76.5 per cent showed serum disease. It does seem to be possible to administer horse serum in large doses intravenously, ten days after an attack of serum disease, without causing more than a mild transitory reaction (48). It is further known that precipitins and indeed anaphylactic antibody (49)(50) may persist in the circulation for many days, after an attack of serum disease, and though experience upon the reinjection of individuals with serum at intervals of a few weeks is very limited, there are observations that suggest that a period of considerable resistance may follow an attack of serum disease. These few available data suggest that this period of comparative insensitiveness corresponds to the period of immunity in animals following repeated injections of protein at short intervals; and that this immunity may be susceptible to the same explanation; namely, the presence of an excess of circulating antibodies that prevents the union of antigen with the cells of the body.

Desensitization of the naturally hypersensitive state in man. Since the report in 1909 of Gillette (51) who collected accounts of 30 cases of sudden collapse or death following the first injection of diphtheria antitoxin, there has been considerable and increasing interest in the forms of hypersensitiveness, already alluded to, which occur in hay fever patients, in asthma, in certain acute gastro-intestinal disturbances, in eczema, urticaria, angioneurotic edema and some other forms of cutaneous eruptions. The work of Cooke and Vanderveer (52), Schloss (53), Talbot (54), Blackfan (55), Goodale (56), Walker (57), Rackemann (58), Koessler (59), Scheppergrell (60), Hurst (61), and Free-

man (62), has established in great numbers of cases a direct etiological relationship between a hypersensitiveness toward one or several of a great variety of substances and the symptoms manifested by many patients suffering from these diseases.

From a broad point of view, it seems apparent that hypersensitiveness shown by different people to pollens, animal emanations, foods, drugs, and possibly bacteria, is dependent upon a common pathological state. The symptoms, it is true, arising from this state of hypersensitiveness may vary in different patients, for in one person they may indicate involvement of the respiratory tract, in another, of the gastro-intestinal tract, or in a third, some affection of the skin; but on the other hand, in many reported instances of hay fever, or asthma, there have appeared simultaneously or alternately in the same individual gastro-intestinal disturbances and skin eruptions, and so far no arguments have been adduced to lead one to believe that the fundamental alterations in the tissues of the patient who suffers from hay fever due to ragweed is essentially different from those of a similarily hypersensitive patient who suffers from urticaria or gastro-intestinal disturbances from eating eggs. As a matter of fact the ingestion of a single food, such as eggs, may cause in the same person or in different persons, such varied symptoms as urticaria, eczema, asthma and gastro-intestinal disturbances. The reason why a single substance, such as egg, should cause asthma in one person, urticaria in another and gastro-intestinal disturbances in a third, has not been satisfactorily explained, but the experiments of Auer (63) and an observation of McBride and Schorer (64) suggest that non-specific local irritation may render one organ or tissue of the body more susceptible than another to the reactions brought about in a hypersensitive individual by contact with the specific material to which he is sensitive. Auer found that the tissues of the sensitized rabbit's ear, irritated by the application of xylol, undergo edema and necrosis when the antigen is reinjected intravenously, in doses too small to cause symptoms of anaphylactic shock, while McBride and Schorer record the history of a man hypersensitive to eggs in whom, after eating small amounts of egg white, urticaria appeared only when the skin was irritated mechanically.

A comparison of these types of hypersensitiveness seen in hay fever, asthma, etc., which have often been termed "natural," since their origin is very obscure, both with the artificial hypersensitiveness produced in human beings by the injection of such foreign proteins as horse serum, as well as with the anaphylactic state produced experi-

mentally in animals, discloses, on the one hand, important analogies, and, on the other, brings out differences that have seemed to some investigators to be almost of fundamental importance.

Coca again upholds the view that the so-called allergies are fundamentally different in their nature from the anaphylactic state in animals. It is true that there are at first sight striking differences between the anaphylactic animal and the hypersensitive individual. In the first place the etiology of these natural forms of hypersensitiveness is still obscure, for though it has been shown by Schloss and Worthen (65), Schloss and Anderson (66) and Grulee and Bonar (67) that a fair proportion of infants absorb egg albumen from the gastro-intestinal tract and excrete this protein unchanged in the urine, and by Shannon (68) that suckling infants nay acquire through their mother's milk proteins which form part of their mother's diet, it has not been definitely proven that the parenteral introduction of such foreign proteins may always produce sensitiveness in infants. Indeed Stuart (69) has been unable to confirm the work of Shannon by careful experimentation and has failed to demonstrate egg protein in mother's milk.

There must be some other factor which determines the extreme hypersensitiveness of patients subject to hay fever, asthma, urticaria and similar conditions, for it is known that man is less readily sensitized by artificial methods than many of the lower animals, and it does not seem likely that during the absorption of small amounts of protein through the mucous membranes of the gastro-intestinal tract, or of the respiratory tract or even through the skin could alone produce the exquisite hypersensitiveness which is often observed in the human being, and which may result in the appearance of violent symptoms after the subcutaneous injection of 0.000,001 cc. of antigen.

One other factor that must be considered is the hereditary tendency that many families show to idiosyncrasies of various types. The familiar tendency toward asthma has been frequently alluded to by most writers on this subject. It has now been established that hypersensitiveness to proteins may occur very definitely in families, and Cooke and Vanderveer have brought out the fact that hay fever affects members of families in a proportion which closely approximates the theoretical figures of the Mendelian Law. They suggest that such idiosyncrasies may be inherited as a dominant characteristic. In their study of 504 cases of sensitization, principally to pollens, in which a satisfactory history could be obtained, 48.4 per cent showed some form of sensitization in the direct or collateral antecedents. The history was positive for one

side of the family alone in 205 cases and for both sides in 39 cases. Rackemann (70) found, in a study of 150 cases of asthma, that a history of asthma, hay fever, or food poisoning in the immediate family could be obtained in 58.7 per cent of the cases that showed hypersensitiveness to foreign proteins, but in only 10.5 per cent of the instances that were not demonstrably hypersensitive. Walker has likewise emphasized the familial tendency to hypersensitiveness in asthmatics. Striking examples of familial idiosyncrasies have been reported by Talbot, while Laroche, Richet and St. Girons (71) have reported a family in which an idiosyncrasy to eggs ran through four generations and occurred usually in the male members. Adkinson's (72) very careful analysis of the factors of inheritance in 400 cases of asthma, studied by Walker, brings out many important points. It was found that 48 per cent of the cases gave a history of the occurrence of asthma among other members of the family. In the group of 191 of these patients that were found sensitive to protein, 52 per cent gave a history of asthma in the family, while in the non-sensitive group 41 per cent knew of the occurrence of asthma or hay fever in the family. It was further found that many of the asthmatic families contained both sensitive and non-sensitive individuals, though sometimes sensitization ran definitely in families. In the instances of familial sensitization, the sensitization was not identical as regards the specific proteins or the clinical symptoms in different members of the same family. Adkinson concludes that the tendency to asthma acts as a true inherited trait, and may be transmitted as a dominant or as a recessive characteristic. In the extreme dominant, where both parents have asthma or hay fever, all the children tend to develop the condition, whereas in the extreme recessive, when both parents are normal but one is simplex, half the children would be simplex and bear the asthmatic characteristic recessive in their germ plasm. The results of all these studies and observations seem to establish the fact with considerable assurance that a condition of the tissues, at least, may be inherited that renders the individual highly prone to the development of hypersensitiveness. The idiosyncracies themselves may differ in the different members of the same family and may assume quite different forms of expression. Occasionally, all members of the family may have hay fever, but in some it may be caused by ragweed and in others by timothy. On the other hand, one member may have hay fever, another horse asthma, and a third egg eczema and urticara.

The age incidence of the condition of natural hypersensitiveness has been a subject of considerable study. Most observers have pointed

out the fact that it is during the first few decades of life that the manifestations of the spontaneous hypersensitiveness usually occur, and that it is likewise during this period that the tissues react most violently to the application of the protein or foreign substance to which they may be hypersensitive. Walker was rarely able to detect specific hypersensitiveness in asthmatics over the age of 50 and finds that the detection of hypersensitiveness is most readily accomplished in the first and second decade. Rackemann (73) emphasizes the same fact and Latham and Coke (74) state that the onset of symptoms of sensitization in the 270 cases of asthma that they studied was rarely after the age of 30. Coca (75) has compared the age incidence of serum disease and of dermatitis venanata with that of the natural allergies. From observations and theoretical calculations he concludes that 11.6 per cent of the potentially susceptible individuals present symptoms by the fifth year; 27.8 per cent present symptoms by the tenth year; 43 per cent by the fifteenth year, and that by the forty-fifth year practically 100 per cent of the hypersensitive individuals have manifested this state by some symptom. On the other hand the age incidence of dermatitis venanata increases greatly from childhood to adult life at which time it reaches a high figure affecting 90 per cent. The susceptibility to serum disease is quite different from either of these, for according to Coca's statistics all ages are equally affected and the incidence shows practically no variation in the different age groups.

Another characteristic of the individual who shows these idiosyncrasies is that his tissues are likely to react to more than one substance, and as a rule about one-half of the patients show what has been termed multiple sensitization. (Cooke and Vanderveer, Walker, Caulfield, Longcope, Rackemann.) The variety of material which calls forth these reactions and which is known to produce the symptoms in many of these hypersensitive individuals, is very great and is not confined to to the proteins themselves or to those substances producing antibodies when injected into animals. Not only are reactions obtained to protein containing substances but symptoms may also be produced and skin reactions obtained from the use of a variety of drugs and chemicals. Since these latter substances contain no protein, as far as one can determine, it is difficult to explain their action upon the same hypothesis as that used to elucidate the anaphylactic reaction in animals.

Though multiple sensitizations are common in the idiosyncrasies and occur in 50 per cent, the groups of substances to which the patients are sensitive are not always of one type, and though certain individuals

may react to several varieties of plant pollen (52) and others to the protein of eggs or to the extract of vegetables only, this is by no means uniform, and frequently individuals are encountered who may react not only to pollens but to the extract of animal dust and to egg albumen (54), (57), (53), (100), (58). Also, in spite of these multiple reactions, there seems often to be a specific selection among different proteins which go to make up a complex substance such as egg white, cereal seeds or animal hairs. The patient may show a typical reaction with ovomucin, but none to conalbumin (Schloss), a typical reaction to wheat proteose, but none to wheat gliadin or leucosin; to horse dander, but not to horse serum; or to the peptone of dog hair, but not to the alkali metaprotein of dog hair, or vice versa (Walker). It is difficult therefore to understand this multiple sensitization on the basis of a group reaction or upon the basis of non-specific sensitization.

It is interesting, too, to note that the presence of circulating antibodies in these naturally hypersensitive individuals is extremely rare. Isolated reports are on record of specific precipitation, of complement fixing antibodies and of passive transfer of sensitiveness to guinea pigs with the serum of individuals who show idiosyncrasy to such varied antigens as pollen, egg white and the extract of horse dander (76), (77), (59), (78), (79); but many observers have failed consistently to obtain such results (80), (81). One instance has been reported by Ramirez (82) of possible transfer of hypersensitiveness to horse dander by transfusion of blood from one human being to another, and if this, by accident, should be repeated, it would have important bearing on this entire subject.

From the data that have accumulated one must conclude that natural idiosyncrasies for allergies which occur toward various proteins and even non-protein substances, such as drugs, differ in many respects from anaphylaxis in animals and indeed from the artificial sensitization in man, the proteotype of which is serum disease, so that one cannot at the present time be sure that this group of individuals who so frequently suffer from hay fever, asthma, eczema and urticaria ought to be considered in the same category as animals sensitized to foreign proteins. On the other hand, there are many similarities as Dale (83) has recently pointed out, and if one assumed that the cells of these individuals for some reason attained a very high degree of sensitiveness sometimes to one, sometimes to several antigens, the fundamental condition existing in these hypersensitive individuals would be analogous or almost exactly the same as that which is observed in the sensitized guinea pig.

Like the specifically sensitized animal, these individuals may also be desensitized. The early attempts of Noon (84), Freeman (85) and Clowes (86) to render patients with hay fever refractory to inhalation of the specific pollen to which they were sensitive was soon repeated by Goodale (87), Koessler and Cooke (88), and have been greatly extended and amplified especially by Cooke and Vanderveer, Walker, Rackemann and others. These workers have established the fact that a certain proportion of patients may be relieved of their symptoms partially or entirely by injecting subcutaneously minute quantities of extracts of the pollens, to which they are hypersensitive, in increasing doses at 5 to 7 day intervals. To be effective, the injections must be started several months before contact is likely to occur with the specific pollen, and must be continued for weeks or months. Vanderveer (89), reporting on 2000 cases of hay fever, states that 25 per cent of cases are entirely relieved of symptoms, 50 per cent of patients are made comfortable, 15 per cent are slightly relieved and 10 per cent are not helped. Somewhat similar results have been obtained by Walker (90) and by Rackemann (91). Though the proportion of cases of asthma sensitive to animal dust, pollens and foodstuffs that may be relieved by this method of treatment is somewhat smaller, still a certain number show improvement of symptoms following this method of treatment (92). Not only may this hypersensitiveness be reduced by subcutaneous injections, but it may also be brought about by local application of the specific substance to mucous surfaces; for Schloss (93) showed that a child, who was highly sensitive to the ingestion of egg white, could be rendered refractory by feeding him small quantities of ovomucoid in capsules. The dose was gradually increased so that at the end of 2½ months the child was able to eat eggs without symptoms. This observation, confirmed by Talbot (94), has been employed repeatedly with success not only with eggs but with milk and other food substances (95), (96), (97). It is not only in the cases of alimentary sensitiveness that application to the mucous surface of the specific substance causing the reaction brings about desensitization, for it seems probable that certain forms of hypersensitiveness of the respiratory tract may be relieved by the direct application of the specific antigen to the nasal mucosa. The experiments of Sewall (98) showed that the local application of horse serum to the nasal mucosa of guinea pigs may sensitize the guinea pig both locally and generally, and that repeated nasal installations of small amounts of horse serum would sometimes result in desensitization of the nasal mucosa without impairment of the

general sensitiveness. Similar observations have been made by Ulrich who employed in his experiments pollen extract and pollen-dust. Mackenzie and Baldwin (99) have employed a somewhat similar procedure in an attempt to desensitize patients with hay fever by local application to the nasal mucosa of pollen extract. They find that the reactivity of the nasal mucosa may be markedly diminished by spraying the nose and throat with the specific pollen antigen, and that the results compare favorably with those obtained by giving repeated subcutaneous injections of the pollen antigen. Caulfield (100) is inclined to uphold this view. The most satisfactory evidence that the repeated local application to a tissue of an antigen results in diminished reactivity of this tissue is to be found in some experiments of Mackenzie and Baldwin (101). They were able to render a local area of the skin, which was hypersensitive to different antigens, insensitive to these antigens by applying, at short intervals, solutions of the antigen to a given area; while the skin only a short distance from this selected spot retained its original hypersensitiveness. This local exhaustion of the reaction was found by them to be specific but of short duration, lasting only 24 to 48 hours. Cooke (102) in repeating these experiments points out that the local exhaustion of the reaction is only relative, and that when the area no longer responds to a high dilution of antigen it may still react to a stronger dilution. In his experiments the exhaustion was not absolutely specific.

The materials, such as foods, pollens and animal emanations to which patients may be hypersensitive usually contain protein, and can therefore be considered as true antigen; but hypersensitiveness is often observed to chemicals and drugs that obviously are not protein in nature, and, therefore, cannot be considered antigens in the ordinary sense of the word. In spite of this fact patients hypersensitive to drugs may respond with cutaneous reactions and general immediate symptoms from the local application or ingestion of drugs as they do to pure proteins (103). Such patients are likewise susceptible to desensitization and may be made refractory to quinine (104), (105), (106), to antipyrine (107), as well as to the other chemical substances by repeated doses of minute quantities of the specific drug to which they are hypersensitive.

There is abundance of proof, therefore, to show that individuals who are spontaneously hypersensitive to such varied substances as pollens, animal emanations, foods and chemicals such as alkaloids and crystalloids may, by various methods of application of the specific substance,

be rendered partially or almost completely insensitive to fairly large doses of the material which, before treatment, would have caused definite or violent symptoms. The relative degree to which this state of desensitization may be carried is illustrated by records of a case published by Alexander (108). This patient, an asthmatic, suffering with pneumonia was found to be spontaneously hypersensitive to horse serum and to extracts of horse hair. By fractional dosage such large quantities of antipneumococcus horse serum as 65 cc. could be administered intravenously without producing more than mild symptoms of asthma. Although this patient was rendered refractory to large doses of horse serum, the records show that there was not complete abolition of the hypersensitive state, and Cooke (109) from his wide experience concludes that it is practically impossible to render a patient who is spontaneously hypersensitive to a given substance completely refractory to very large doses of this material. To uphold this view is the fact that patients undergoing desensitization may frequently react with considerable violence to injections of the antigen when the doses are increased too rapidly. Indeed all who have employed this method have warned against these reactions (110), and Vanderveer states that in 1 to 2 per cent of his cases severe reactions occurred during the process of desensitization.

The desensitization or hyposensitiveness is only of temporary duration. In the local skin desensitization obtained by Mackenzie and Baldwin it lasted but a few days. In the case of antipyrine sensitiveness reported by Widal and Vallery-Radot, the sensitiveness was greatly reduced by administering repeatedly small doses of the drug, but recurred 43 days after the last desensitizing dose. It is well known that the relief which hay fever patients obtain, after a series of inoculations, rarely lasts for more than one season (Cooke, Vanderveer, Walker). It is usually easier to accomplish desensitization the second year than it is the first.

Since the mechanism of the sensitization or the allergy in the spontaneously hypersensitive individuals is not clearly understood, it has been found difficult to explain the process of desensitization. It seems clear that the desensitization may be highly specialized and that desensitization may be as specific as it is in the anaphylactic guinea pig.

The state of desensitization is not known to be accompanied by the presence of specific antibodies in the circulation (Cooke, Floyd, Coca and Rackemann). But this problem has been somewhat opened again by the observations of Wood (111), who found that during desen-

sitization both of dogs and of patients hypersensitive to the choroidal pigment of the eye, specific complement fixing antibodies appear in the circulation. The sensitization to pigment which occurs in these patients may be more nearly like the artificial sensitization to injections of horse serum than it is to the spontaneous hypersensitiveness of asthma and hay fever, and it would therefore be improper to draw conclusions from Wood's experiments that could be applied to the latter group of cases.

Coca, Floyd and Cooke (112) drew the conclusion from their experiments, devised to produce anaphylaxis in guinea pigs with extracts of ragweed pollens and of horse epithelium, that the phenomenon of desensitization in the hay fever patient is dependent upon an antigen-antibody reaction and that it is essentially the same as the desensitization of the guinea pig anaphylactic to horse serum. Later, however, Coca dismissed this view as lacking in proof. Though proof of an antigen-antibody reaction is difficult to establish, there are many analogies between the phenomenon of desensitization in the specifically sensitized guinea pig and the naturally sensitive hay fever or asthmatic patient, and it does not seem unreasonable to suppose, as some observers have, that during the period of desensitization a reaction takes place between the antigen and some form of antibody in the cell, during which process the antibody in the cell is reduced in amount or partially exhausted. As the exhaustion becomes greater, larger and larger amounts of antibody are required to call forth a reaction. When, by cessation of the injections, antigen is no longer furnished, the reacting substance in the cells returns, as it does in the anaphylactic guinea pig, and hypersensitiveness is reëstablished.

NON-SPECIFIC DESENSITIZATION. There are other theories, however, that have been presented more recently and which are based upon the conception that desensitization may be brought about by non-specific as well as by specific measures. It was originally shown by Besredka that the symptoms of anaphylactic shock in the guinea pig might be suppressed or reduced by narcotics. Ether, chloral, chloroform, alcohol and ethyl chloride were all more or less effective in diminishing the symptoms of shock or preventing the death of the animal; and he supposed the result was dependent upon a lowering of the sensibility of the animal to the effects of the anaphylactic shock. Friedberger and Hartoch (113) demonstrated that a dose of 0.1 to 0.3 gram of sodium chloride, given immediately before the shocking dose of protein, will protect sensitized guinea pigs against a full lethal dose of the specific protein. C. Richet, Brodin and F. Saint-Girons (114), from their experi-

ments upon the action of sodium chloride in suppressing anaphylactic shock in dogs, conclude that it is due to a saturation of the cells of the body by sodium chloride which makes them impermeable to the hypothetical poison produced during anaphylactic shock. More direct evidence to explain the protective action of sodium chloride has been brought forward by Dale and confirmed through some experiments with proteotoxins by Zinsser, Lieb and Dwyer (115). These experiments showed that the addition of sodium chloride to the solution in which the uterus from a sensitized guinea pig is suspended, rendered the muscle refractory, and prevented the contractions that usually occur upon the addition of the specific protein to which the animal is sensitized. It seems probable that the inhibition of the reaction under these circumstances is due to the lessened irritability of the muscle cells.

It has further been observed that many chemicals when injected immediately before the intoxicating dose of specific protein will abolish or reduce the symptoms of anaphylactic shock in guinea pigs and dogs. Biedl and Kraus (116) observed such an effect with barium chloride, Lumiére and Chevrotier (117) with sodium sulphate, Brodin and Huchet (118) with a combination of formaldehyde and hydrosulphite of sodium, Kopaczewski (119) with cocaine, saponin, soaps, biliary salts, alkaline carbonates, saccharose and glycerine; Van Geertryden, Bernard and Zunz (120) with hirudin, and Archard and Flandin (121) and Duprey (122) with injections of lecithin.

A possible explanation for the protective action of some of these alkaline salts, which has also been observed by Sicard and Paraf (123) and which, in the form of intravenous injections of sodium carbonate, has been employed by them as well as by Widal, Abrami and Brissaud in the treatment of serum disease, may be found in some experiments by Eggstein (124), who discovered, that, during anaphylaxis in dogs, there occurs a reduction in the carbon dioxide capacity of the serum which appears at the first symptom and falls progressively during shock, often reaching as low a figure as 25 volumes per cent. If recovery occurs the carbon dioxide capacity of the serum returns to normal within 6 hours. Though German (125) was not able to confirm these observations during anaphylactic shock in rabbits, Hirsch and Williams (126) have noted a considerable decrease in the CO_2 combining power of the plasma during anaphylactic shock; and, by the gas chain method, have found a change in the pH of the blood to the acid side which was notable in some instances and showed a reduction that was as great as from 7.8 to 6.88. These observations, though somewhat conflicting, would indi-

cate that a pronounced acidemia develops during anaphylactic shock, and that the administration of alkaline salts at this time is followed by some amelioration of the symptoms. It seems improbable, however, that the acidosis can be looked upon as anything more than a symptom, and a sequel to more profound alterations that take place in the cells and tissues of the body. Other chemical changes may occur in the serum at the same time for Stern and Reiss (127) state that the blood lipoids and neutral fats of the serum decrease during anaphylactic shock in dogs.

It has been generally assumed by many that the action of most of the chemicals, which, so to speak, are non-specific in their action and purely transitory in their effect, is directed toward the relief of symptoms or toward rendering the tissues of the body more resistant to the effects of the hypothetical toxin produced. They protect the animal or individual in much the same way as do adrenalin and atropin. More recently, Kopaczewski (128) has advanced the view, that many of these chemicals have, in common, an effect which, he believes, is of fundamental importance in preventing anaphylactic shock. In studying the production of anaphylatoxin, Kopaczewski (129) found that the toxin could be produced from blood serum by the rapid contact with gels at 0°C. He concluded that the formation of this substance could not be dependent upon ferment action. Observing that a conglomeration of particles occurred in the serum during the formation of anaphylatoxin, he conceived the idea that the transformation of a bland serum into a toxic serum was caused by this flocculation. The flocculation of colloids is attended by certain physical changes in the serum which he considers to be of much importance. These changes consist in a lowering of the surface tension and increase in viscosity of the blood. Upon the basis of these experiments he has constructed an hypothesis to explain the production of anaphylatoxin shock and anaphylactic shock, as well as of desensitization. In this, he assumes that, during shock, there is a rupture of the colloidal equilibrium that is expressed by flocculation of particles. He finds that chemicals, which prevent the lowering of surface tension of serum, inhibit the formation of anaphylatoxin in vitro, and possess some power to inhibit the symptoms of anaphylatoxin shock or anaphylactic shock in vivo. Though saponin and the soaps are particularly effective in this respect, he believes that most of the chemicals, that exhibit an ameliorative action in anaphylactic shock, owe their power to this particular property.

Since the hypothesis rests upon the detection of certain physical changes in the serum, rendered anaphylatoxic in vitro, it is important that these observations should be repeated. Zunz and LaBarre (130) state that they have observed the same changes in the surface tension and viscosity of the serum during anaphylatoxin formation; but Dale and Kelloway (131) have been unable to detect, by accurate methods, any change in the surface tension or viscosity of blood serum rendered toxic by incubation with starch.

Though questioning the details of some of Kopaczewski's work, many of the recent French writers are inclined to conceive of a physical change as the essential feature of anaphylactic shock. Widal, Abrami and Vallery-Radot (132) have adopted the view that the symptoms do not depend upon the production of a poison but arise from physico-chemical changes in the equilibrium of the body fluids and cells. They believe that in anaphylatoxin shock the rupture of the colloidal equilibrium or "colloidoclasie," as they term it, takes place in the blood serum, while in specific anaphylactic shock it proceeds within the body cells. They take exception to many of Kopaczewski's ideas but agree in considering that the process is not fundamentally specific in nature, and advance the view that any substance that brings about the rupture of colloidal equilibrium, to a slight extent or by slow degrees, will prevent the explosive rupture which induces the condition of acute anaphylaxis. They do not seem to make any differentiation between the specific desensitization, as developed by Besredka, and the non-specific inhibition of anaphylactic shock, and conclude that the mechanism in both is the same.

A practical application of this hypothesis is to be found in the work of Pagniez and Vallery-Radot (133) who advocate the administration of peptone in capsules by mouth to prevent the urticaria or other symptoms caused by eating foods to which the individual is hypersensitive.

A type of non-specific desensitization brought about by the use of organic compounds was first described by Biedl and Kraus (134) who stated that animals, sensitized to a specific serum, could be desensitized with heterologous substances such as peptones. Besredka, Strobel and Jupille (135) were unable to confirm this particular observation in guinea pigs, and Besredka (136) more recently, in attempting to differentiate anaphylatoxin shock from anaphylactic shock, found that sensitized guinea pigs, rendered immune to the injection of suspensions of agar as described by Bordet (137), showed no reduction in their sensitiveness to the specific protein.

The literature, however, contains many observations that uphold, in a general way, the observation of Beidl and Kraus, and that indicate that the intravenous injection of heterologous proteins in animals, specifically sensitized, diminishes the sensitiveness to injections of the specific antigen. Experiments upon the specific desensitization of animals treated with two or more separate proteins, has brought out the fact that desensitization to one protein may render the animal somewhat less sensitive to the second. Bessau (138) sensitized guinea pigs to two different antigens and after producing shock by the reinjection of one antigen tested the sensitiveness of the guinea pig to reinjection of the second. He found that the sensitiveness of the guinea pig was materially reduced, under these circumstances, to the second antigen, as measured by the controls; and that this partial desensitization increased with the severity of the shock caused by injection of the first antigen. In later experiments (139) he measured more accurately the effects of the shock induced by the first protein in desensitizing towards the second and found that the period of desensitization persisted for 14 days. Friedberger, Szymanowski, Kumagai and Odaiva (140), who studied this problem extensively, concluded that though specific desensitization, under the above conditions, can be carried out to relatively high degrees it is not absolute. Dale and Hartley (155) have observed that the uterus of a guinea pig sensitized to two different antigens reacts, in vitro, more violently upon the addition of the first antigen than upon the addition of the second; and though reactions are obtained, which are to a high degree specific, the primary contraction of the uterus does effect to a certain extent the reaction of the uterus to the second antigen, so that in many instances the maximum effect is not obtained. Marsini, (141) using the intestinal strip of the guinea pig to detect desensitization in guinea pigs sensitized to two antigens, came to the conclusion that there was both a specific and an aspecific "antianaphylaxis." Brack (142) has recently reinvestigated this problem. He sensitized guinea pigs with rather large doses of three antigens, sheep serum, horse serum and human serum; and employed the intestinal muscle strip to measure the degree of sensitization. He found that application of one antigen, which produced a maximum contraction of the muscle, rendered the muscle much less sensitive than the control to application of the second antigen; while the muscle which had contracted upon the application of two different antigens responded very feebly to the third. He suggests that the phenomenon may depend somewhat upon a diminished reactivity of the smooth muscle to any form of stimulation.

But this cannot explain the phenomenon entirely, for in other experiments a similar, though not quite so marked, reduction in sensitiveness to application of the second protein could be obtained by repeated additions of small quantities of the first antigen, insufficient to cause contractions, but in aggregate, enough to bring about complete desensitization to the first protein. It seems impossible to avoid the conclusion that in animals sensitized to two proteins, anaphylactic shock to one reduces temporarily the sensitiveness to the second.

The same effect as that noted in experiments upon double sensitization and desensitization may, indeed, be obtained by the injection of large doses of heterologous proteins, for Pfeiffer and Mita (143) were able to protect guinea pigs, sensitized to horse serum, against a lethal dose of this antigen by a previous injection of beef serum. Beef serum seems to be much less likely than horse serum to cause serum disease in human beings. This has been pointed out by Kraus, Cuenca and Sordelli (144) and it has therefore been advocated by Kraus (145) that cattle be used for the preparation of antitoxic sera. Calvary (146) states that some of the effects of specific anaphylactic shock in dogs, such as the increased flow of lymph and the drop in blood pressure, can be inhibited by an injection of beef serum made previous to the injection of specific antigen. Benjamin and Witzinger (147) observed quite definitely the partial inhibition, by injections of heterologous sera, upon anaphylactic shock following the injection of the specific antigen. Brack records similar observations. Karsner and Ecker (148) have recently reviewed the entire subject of non-specific desensitization by the use of heterologous sera upon anaphylactic shock following the injection of the specific antigen. Beef, swine, ox, sheep, rabbit and human sera were chosen as heterologous sera. Since the minimal lethal dose of horse serum was not determined in their experiments, it was difficult or impossible to measure the effectiveness of desensitization by homologous sera, but this was found frequently to be considerable. They noted, however, that, to a certain extent, desensitization could be accomplished by the use of heterologous sera; and that the most effective way of inducing the non-specific effect was through intravenous injection. The heterologous desensitization developed with as great rapidity as the homologous desensitization but was of distinctly shorter duration. Dale (149) has devoted some attention to this problem of non-specific desensitization and accepts its accomplishment as a fact. Kelloway and Cowell (150) have confirmed some of the previous observations upon the desensitizing property of anaphylatoxin for guinea

pigs actively sensitized to a single protein. The anaphylatoxic serum which they employed was prepared from guinea pig serum, and, during the experiments, they noted the interesting fact that the intravenous injection of normal guinea pig serum into actively sensitized guinea pigs, causes a definite protection against the specific antigen which, however, is of short duration. By employing the uterine strip preparation, they could show, that this loss and subsequent return of sensitiveness of the anaphylactic animal, ran parallel to, and could be explained by changes in the sensitiveness of the smooth muscle. They consider that these changes are due to physical alterations in the muscle cells.

Though it seems quite clear from many of the foregoing experiments that the active sensitization to one antigen may be temporarily reduced by the intravenous injection of heterologous proteins, as well as of toxic substances derived from proteins, and, though it is evident that demonstrable intoxication by these heterologous proteins and anaphylatoxins, is not essential for the partial desensitization, the exact explanation of this non-specific effect is still obscure. It is usually spoken of as desensitization, but there is no direct evidence to show that these preliminary injections produce an effect upon the specific antibodies residing in the body cells.

Doerr has pointed out the fact that if complex antigens, such as animal sera, are employed to immunize rabbits for the production of precipitating sera, crossed or group reactions are not uncommonly encountered, especially when the animals are highly immunized. These group reactions are more frequent when the sera of nearly related species are used in the tests. Consequently, when complex antigens are employed for double sensitization and desensitization, it is conceivable that crossed or group reactions may be encountered, and that during the anaphylactic shock, caused by the injection of one antigen, a certain proportion of the antibodies to the second antigen may be neutralized or destroyed. These group reactions are, however, almost entirely eliminated when pure antigens are employed (151). The most suggestive experiments dealing with this point are those of Kellaway and Cowell. They observed that the intravenous injection of normal guinea pig serum into guinea pigs, immunized against horse serum, resulted in an immediate and marked decrease in the circulating antibodies. This resulted in an enhanced sensitiveness to injections of the specific antigen of guinea pigs that were immunized, were known to contain a high titre of circulating antibody, and that could be shown, by controls, to be quite refractory to injections of the specific antigen.

This enhanced sensitiveness occurred during two periods; first, shortly after the intravenous injection of normal guinea pig serum and secondly after the restoration of the sensitiveness of the plain muscle, but before the return to normal of the demonstrable circulating antibody. These experiments are highly suggestive of a direct action of the herterologous serum upon the specific antibody.

There are, however, other factors of importance that must be considered. These have to do with certain antagonistic effects that have been observed between two foreign proteins when they are injected simultaneously or in rapid succession. The early experiments of Benjamin and Witzinger showed, that when two antigens are injected into a normal animal simultaneously or in succession, they may call forth unequal reactions on the part of the body. This is particularly true when one antigen is in excess of the other. They showed in guinea pigs that when an injection of a large dose of horse serum was followed, in 24 hours, by a smaller dose of beef serum, sensitization to the beef serum is inhibited or suppressed. Weil (152) has found that several injections of large amounts of heterologous serum will prevent passive sensitization of guinea pigs to a specific immune serum. He injected normal rabbit serum or sheep serum into normal guinea pigs, and found that, for 24 hours to 14 days following these injections, the guinea pigs could not be passively sensitized to horse serum by the injection of serum from rabbits immunized to horse serum. As an explanation, he suggested that the large amounts of rabbit serum or sheep serum saturated the receptors capable of forming antibody against foreign protein, so that a union, between the horse serum antibody and the cells could not take place. Julian Lewis (153) has shown very clearly how marked may be the inhibiting effect of the injection of large doses of serum, from one species, in preventing active sensitization in guinea pigs against small doses of serum from other species. Thus an injection of 2.0 cc. of dog serum inhibited active sensitization of guinea pigs to an injection of 0.3 of horse serum. This inhibitive action may take place when both foreign sera are injected together.

Some recent work of Doerr and Berger (154) goes to show that this effect is not altogether a quantitative one. They have studied the anaphylactic reactions in guinea pigs to four different protein fractions of horse serum, namely Euglobulin, Pseudoglobulin, Albumin C and Albumin D. They worked principally with Euglobulin and Albumin C, and found that guinea pigs could be readily and specifically sensitized to these two fractions, but that for animals sensitized to equal amounts,

the intoxicating dose of Euglobulin was considerably smaller than that for Albumin D. A guinea pig, injected simultaneously with equal quantities of Euglobulin and Albumin D, became equally sensitive to the two proteins; but, when one antigen was in excess of the other at the primary, injection, though both were given simultaneously, very interesting results were obtained. It proved that an excess of Euglobulin inhibited sensitization to Albumin D, but the reverse was not true; and an excess of Albumin D did not prevent sensitization to Euglobulin.

It is possible that such experiments with purified proteins will throw considerable light upon the problem of non-specific desensitization and the inhibition of sensitization. Heretofore most experiments directed toward the elucidation of the problem have been carried out with such complex substances that it is difficult to unravel and explain the results that are sometimes discordant. It seems highly probable, that the cells of the body do not react, with the same degrees of intensity and of rapidity, toward different proteins; and for a proper understanding of this whole question it is essential that further information should be obtained upon these important biological and chemical reactions. Dale and Hartly (155) have shown, that, when guinea pigs are sensitized to serum globulin or to serum albumen, there is a distinct difference in the time interval required for the appearance of sensitiveness of the uterine muscle to these two proteins. The sensitiveness to serum albumen appears several days before that of serum globulin. Doerr and Berger (156) have extended their experiments upon the fractions of horse serum and find that there are distinct biological differences between the activity of these fractions. These consist in differences in the size of the minimal sensitizing dose of the proteins, which was found to descend in the scale from Euglobulin to Albumin D; in differences in the incubation period, which, for a given amount of protein, was found to be shortest for Euglobulin and longest for Albumin D; and in differences in the amounts of protein required to produce anaphylactic shock in actively sensitized guinea pigs. Euglobulin produces shock in the smallest doses; Albumin D in the largest.

It can be seen from this review that many of the details of the mechanism of desensitization of animals or of human beings, actively sensitized by the injection of specific protein, and of animals, passively sensitized to specific proteins, are imperfectly understood; but most of the experimental evidence points to the fact that, during the process of specific desensitization, there is a neutralization or destruction of antibodies situated in the cells of the animal. To accomplish complete

destruction or neutralization of these antibodies is extremely difficult in highly sensitized animals or human subjects.

Suppression of anaphylactic shock, which has an entirely different significance from desensitization, may be brought about by various methods, depending in some instances, upon the reduction of reactivity of the tissues of animals to the intoxicating factor of the shock itself; and accomplished in other instances by placing a barrier between the cells of the body and the specific antigen which is injected.

It is possible that the so-called non-specific desensitization, brought about by the injection of heterologous protein substances into the specifically sensitized animal, may, in certain instances, when the complex and mixed proteins, such as animal sera, are used for sensitization, depend upon some type of group reaction in which the antibodies in the cells are saturated or neutralized by fractions of heterologous proteins employed. It is also possible to conceive of these heterologous proteins as interfering, in some way, with the union of the specific antigen and the specific cellular antibody. This may be a phenomenon which is analogous to the interference which an injection of large quantities of heterologous proteins has upon the specific sensitization of the animal tissues by the subsequent injection of a single specific antigen.

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ANHYDREMIA

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When the amount of water eliminated from the body exceeds the amount ingested, plus that produced through metabolic processes, a certain degree of desiccation of the various organs, tissues and fluids occurs. The body possesses an available store of water which exists for the greater part in the muscles and in the skin, and which can be drawn upon to some extent before any considerable degree of desiccation of other parts of the body occurs. As larger amounts of water are withdrawn a drying out of all parts of the organism takes place, but the degree of desiccation varies markedly in the different organs. The fatty tissues, brain, heart and skeleton lose relatively little water as compared with the muscles skin and blood. (Falk and Scheffer, Volkmann, Nothwang, Straub, Durig, Engels, Tobler.) The muscles which compose 42.8 per cent of the body weight give up 67.89 per cent of the total water lost (Engels). The withdrawal of fairly large amounts of water from the muscles (10 to 20 per cent of their total water) fails to impair their function, as determined by electro-motor activity of the excised muscles (Durig), nor is there any apparent morphological change (Durig, Straub). The skin also seems to be but little damaged functionally or structurally by the loss of a considerable portion of its water content. In the case of the blood, conditions are quite different. Here desiccation to even a slight degree results in impairment of the circulation and, as a result, to secondary functional disturbances of almost every part of the body. There is an alteration in the metabolic processes and, when sufficient concentration of the blood occurs, a disturbance of the heat-regulating mechanism. As most of the observed physiological effects of loss of water are referable to the concentration of the blood, and as the condition of the blood serves as a fair index of the degree of dehydration of the body as a whole the subject of desiccation in general may very well be considered from the standpoint of desiccation of the blood, or *anhydremia.*

The experimental production of anhydremia. Anhydremia may be brought about by restricting the water intake or by increasing the output through various channels.

Some animals, for example, moths, serpents and camels, can exist for very long periods without any intake of water. Other animals under the conditions of hibernation live without water intake for long periods. Most animals, however, when living under otherwise normal conditions develop anhydremia within a relatively short time when deprived of water. When a marked degree of anhydremia is brought about death occurs. A man has been known to survive as long as 18 days without food or water when under average conditions of temperature and humidity. Under the same conditions dogs ordinarily live from 14 to 66 days when deprived of all food and water (Keith, Poletayeff, Underhill); rabbits live from 14 to 17 days (Utheim); pigeons usually die within 6 days (Nothwang).

Ingested fluid does not represent the sole available source of water of the body, as appreciable amounts of water are produced during the processes of metabolism. When carbohydrate and fats are burned in the body, all of the hydrogen is converted into water as is also a considerable portion of the hydrogen of protein. It has been calculated by Nobel and by Magnus-Levy that 100 grams of fat give rise to 90 to 110 grams of water, 100 grams of carbohydrate to 55 to 60 grams of water and 100 grams of protein to 40 to 45 grams of water. The amount of water produced in this way serves in part to supply the needs of the body, but in the case of most animals is in itself entirely insufficient. When animals take neither food nor water by mouth a utilization of stored glycogen and fat occurs, there is also some destruction of body protein. In this process a certain amount of loosely bound water is liberated. One gram of glycogen as it exists in the body is combined loosely with about 4 grams of water. Protein is united with approximately the same amount of water. Fatty tissues are relatively dry, there being only about 0.2 gram of water to each gram of fat (Bozenraad). All of this loosely combined water is liberated and becomes available when the protein, carbohydrate and fat of the body are "burned" to supply the needs of the starving organism.

In warm-blooded animals life cannot be maintained unless there is a constant elimination of a considerable amount of water and this elimination takes place even though it may necessitate a desiccation of the body tissues and fluids. Loss of water by evaporation from the respiratory tract and mouth is inevitable unless the air breathed in is saturated with water vapor at body temperature. Evaporation brought about in this way serves the useful purpose of dissipating a part of the body heat. A somewhat larger portion of the body heat

is usually dissipated by evaporation of water from the skin. The amount thus evaporated varies tremendously according to the environment. When the external temperature is equal to that of the body (98.6°) or above it, no heat is lost by conduction or radiation and the only means available to dissipate the heat of metabolism is that of water evaporation. Hunt has calculated that an adult with a metabolism of 3500 calories a day would, at an environmental temperature of 37°C. (98.6°F.), need to evaporate at least 8 liters of water daily to eliminate the heat produced, and to maintain a normal body temperature. This figure makes no allowance for sweat secreted but not evaporated, nor does it allow for the effects of active exercise. Hunt actually found that Europeans in Central India, during the summer season, usually suffered from thirst when the daily water intake fell much below 13 liters a day (200 cc. per kilo per day). Almost all of this water was eliminated from the skin and lungs as the urine volume was small.

The evaporation of water necessary under normal conditions of environment is considerably less than the above. The average adult under average conditions of temperature (65–70°F.) and humidity (35–60 per cent) and while doing light work loses from 30 to 60 grams of water per hour in this way (Benedict and Carpenter, Sonderstrom and Du Bois, Wolpert). This corresponds to from 10 to 20 grams per kilo of body weight per day, or a total of 650 to 1400 cc. daily.

A certain amount of water is required for urinary excretion of waste products, and this amount varies considerably with the character of food material consumed. A sufficient amount of water is excreted to hold in solution urea, salts and other end products of metabolism in a concentration not too great to be capable of secretion by the kidneys. It has been shown by Ambard and Papin and by Adolph that there is a definite maximum concentration of urea and of sodium chloride that can be excreted by the kidneys of each individual, but that the excretion of each substance is quite independent of the excretion of any other. The elimination of 45 grams of urea, or 15 grams of sodium chloride in man requires the excretion of about 1 liter of water. This amount of water, however, will serve for the simultaneous excretion of both substances in the concentrations mentioned. It is thus seen that with a high protein metabolism or salt intake a proportionately large amount of water must of necessity be excreted. In man, on a general mixed diet, the daily urea excretion averages from 30 to 35 grams a day, this would require for its excretion from 650 to 800 cc. of urine per day or about 10 grams per kilo. Adolph found the urinary excretion of an

adult when abstaining from food and water to fall to the low level of 408 cc. per day which was the amount secreted even though the individual was becoming dehydrated at the time. From the above it will be seen that an adult man living under average conditions necessarily eliminates from the body in various ways from 15 to 30 grams of water per kilo per day, or a total of from 1000 to 2000 cc. per day. Under extreme conditions the amount may exceed 20,000 cc. per day. In the case of infants the evaporation of water from the skin and lungs is at least three times as great per kilo of body weight as in adults under the same environmental conditions (Rubner and Heubner). This is necessarily the case on account of the relatively higher total metabolism of the infant. The water requirements of animals for evaporation and urinary excretion vary greatly with the species.

When the intake of fluid is restricted so that this plus the potential water of metabolism is less than the amount eliminated, a certain degree of anhydremia necessarily develops in any animal. Anhydremia has been experimentally produced in man and various lower animals by simple restrictions of water in the diet (Bowin, Durig, Dennig, Engels, Falk and Scheffer, Hunt, Keith, London, Nothwang, Utheim, Schiff, Spiegler, Straub, Underhill, Volkmann).

Dehydration of the body is much more rapidly produced if excessive elimination of water occurs at the same time that the intake is restricted. Czerny produced a high degree of anhydremia in cats by exposing them to warm dry air. Adolph observed anhydremia in man as the result of sweating in a warm room or in a warm bath. Sweating as the result of muscular exercise also favors the development of anhydremia.

Certain drugs, such as pilocarpine, bring about increased secretion of the sweat. Underhill and Roth have observed marked anhydremia in animals deprived of water and injected with pilocarpine.

Excessive removal of water from the body by diuresis results in anhydremia provided the loss is not covered by an increased fluid intake by mouth. Morgulis and Muirhead observed a considerable concentration of the blood following diuresis occasioned by cantharis injection in animals. Numerous investigators have brought about a condition of anhydremia by the administration of sodium chloride or urea by mouth and by intravenous injections of sodium chloride, urea, glucose, saccharose or lactose. All of these substances on excretion in the urine necessarily appropriate water from the body, and if this loss of water is not compensated for by additional intake anhydremia of a severe

grade is produced (Heim and John, Finkelstein, Peteri, Bingel, Straub, Balcar, Sansum and Woodyatt, Keith, Adolph).

An excessive loss of water from the body by way of the intestine follows the administration of the saline cathartics. This loss may be sufficient to lead to a considerable concentration of the blood (Underhill and Errico).

The occurrence of anhydremia in clinical conditions. A certain daily variation in the water content of the body necessarily occurs as the result of such factors as active muscular exercise, exposure to a warm environment or varying intervals of fluid intake. It has been shown by Grunewald and Rominger that the blood is usually somewhat more concentrated in the evening than in the morning.

Severe anhydremia occurs when there is voluntary refusal of water for prolonged periods, for instance in the case of persons mentally deranged. It occurs in individuals exposed to the heat of the desert (King, McGee) and in those working in such locations as deep mines, boiler rooms, etc. (Haldane).

Vomiting brought about from any cause results in a greatly diminished fluid intake and often to a considerable degree of anhydremia. This is especially noted in the case of infants suffering from pyloric stenosis, as no absorption of water takes place from the stomach and relatively little passes beyond the pylorus. Any form of high intestinal obstruction leads to a similar result.

In the presence of diarrhea considerable amounts of water may be lost by way of the stools. Such losses are particularly marked in Asiatic cholera and in the choleriform diarrheas of infancy. In such cases anhydremia rapidly develops and may be severe enough to lead to death in a relatively short period. The amount of water lost by the stools may be enormous and greatly exceed the amount eliminated from the body by all other ways combined (Rogers, Sellards, Meyer, Reiss, Salge, Göppert, Lederer, Lust, Rominger, Marriott, Bessau). As a result of the water loss in severe diarrhea the body weight may be decreased to the extent of 20 per cent or more within one or two days' time (Meyer, Marriott). In the types of diarrhea mentioned the factors of infection and of injury to the intestinal mucosa with a possible change in its permeability complicate the picture and make it difficult to determine to what extent the manifestations observed are due to the anhydremia *per se*.

Severe anhydremia is especially likely to occur in infants. This is due in part to the fact that they have a high water requirement which

must be covered. Furthermore the infant is entirely dependent upon others for water administration, and may be offered an insufficient amount. Newly born infants nursing at the breast and receiving no fluid from other sources frequently become somewhat desiccated due to an insufficient water intake (Crandall, Holt, Müller, Von Reuss, Utheim, Schick, Bakwin, Aron). In any infant the presence of infection is likely to lead to refusal of food, vomiting and diarrhea, with a resulting anhydremia (Marriott).

The composition of the blood in anhydremia. When sudden loss of water from the body occurs the composition of the blood is much more affected than when the same loss is brought about more gradually; thus Adolph observed a concentration of the blood of 15 per cent with a 5 per cent loss of body weight when a subject was rapidly sweated in a hot bath, as contrasted with a blood concentration of only 2 per cent when the same subject lost the same amount of fluid during a period of three hours' sweating in a warm room. Keith observed a concentration of blood plasma of from 24 to 44 per cent and a total blood volume decrease of from 2 to 38 per cent when dogs were rapidly dehydrated by intravenous injections of saccharose solutions, a considerably greater concentration of the blood than is ordinarily observed following a similar decrease in body weight brought about by a more gradual water loss. Sudden withdrawal of fluid from the body results in an immediate concentration of the blood. Later water is given up from the reserve stores in muscle and skin and the blood tends to return to its normal composition providing there is not a continued removal of an excess amount of water from the body (Underhill and Errico). After a period of dehydration the administration of water causes an immediate dilution of the blood and an abrupt fall in the concentration of the hemoglobin (Underhill and Kapsinow, Keith, Rominger). The blood concentration then gradually increases, the excess of water being in part excreted by the urine and in part taken up by the more desiccated tissues. Ultimately if water continues to be administered a condition of equilibrium is finally attained between the tissues and blood after which the concentration of the blood remains constant (Hunt).

Loss of water from the blood necessarily results in an increase in the proportion of the total solids and in the dried weight of a unit volume of blood (Rominger). The specific gravity is increased. There is an increase in the red blood cell count and a corresponding increase in the hemoglobin percentage. The red blood cell count may be almost

twice as high as the normal; thus Czerny observed a count of 10,720,000 red cells in cats made anhydremic by exposure to warm dry air. Bowin also observed a red blood cell count twice that of the normal animal. Underhill and Kapsinow observed an increase in hemoglobin concentration to over 140 per cent of the normal in dogs deprived of water.

Changes in the concentration of the serum proteins of the blood are usually more marked than the red cell concentration as it is from the serum that most of the water is lost (Keith). The serum protein not infrequently increases over 50 per cent in concentration (Reiss, Marriott) a 100 per cent increase has been observed by Behrend and Tenzer in the case of a young infant (serum protein of 11.6 per cent as compared with the normal of less than 6 per cent). Serum protein determinations are readily made by the use of the refractometer (Reiss).

Such high concentrations of serum protein, hemoglobin and red blood cells are usually seen only when anhydremia is suddenly brought about. When a condition of severe anhydremia has lasted for a number of days a decrease in the concentration of hemoglobin and of serum protein occurs even though the body weight and the blood volume determinations may indicate a further loss of water (Lust, Marriott). This may be taken as indication of destruction of blood corpuscles and of serum protein. The experiments of Gürber on frogs, of Utheim on rabbits and Keith on dehydrated dogs show a decrease in the total number of red blood cells in the circulation, when the diminished total blood volume is considered in connection with the cell counts and protein concentration. As a result of this destruction of the blood constitutents an abnormally low cell count, hemoglobin and serum protein content of the blood is often observed following a restoration of the blood volume by fluid administration It is thus seen that determination of the cell count, hemoglobin or serum protein may at times fail to indicate accurately the degree of anhydremia. The same may be said of the determination of the total solids. The measurement of the blood volume taken together with the determination of the other constituents mentioned supplies the necessary data for the estimation of the degree of anhydremia.

The mineral salts of the blood usually show much less change in concentration than does the protein. When the blood plasma becomes concentrated through water loss the inorganic salts are excreted in the urine in such amounts as to maintain an approximately normal salt concentration of the plasma in most instances (Heim and John, Salge, Reiss, Rogers). Some increase in salt concentration of the plasma occurs

when anhydremia is brought about suddenly and also when the anhydremia is of such a degree that renal excretion is greatly impaired. Keith observed a moderate increase of the chlorides of the serum in severe anhydremia. Salge found some increase in the electrical conductivity of the serum in marked anhydremia. Of the individual inorganic salts, phosphates are more likely to be retained than chlorides, when renal activity diminishes as the result of blood concentration (Howland and Marriott). The freezing point of the blood, according to Salge, is lowered, but he attributes this to the increased concentration of organic constituents rather than inorganic salts.

As the result of the concentration of the blood protein and cellular elements the viscosity of the whole blood is greatly increased (Keith, Behrend and Tenzer, Czerny, Lust). The increase in blood viscosity is readily apparent, the blood appears thick and at times syrupy and does not flow readily. McGee states that in a man severely anhydremic as the result of exposure to desert heat, no bleeding occurred from deep cuts on the body.

The total non-protein nitrogen as well as the urea of the blood is high when any considerable degree of anhydremia occurs (Schloss and Stetson, Bang, Minsk and Sauer, Bessau, Valk and DeLangen). A blood non-protein nitrogen as high as 590 mgm. has been observed in cases of Asiatic cholera (Valk and DeLangen). The high non-protein nitrogen of the blood is to be explained in part by the functional disturbance of the kidney as the result of dehydration of the blood and in part by the increased destruction of body protein which is known to occur.

The blood sugar is often higher than normal, thus Schloss observed fasting blood sugar of 0.14 to 0.20 per cent in the case of infants anhydremic as the result of severe diarrhea. Even higher figures have been found recently by the present author. High blood sugar is a common finding in other conditions associated with a low blood volume, for example, in shock (Cannon). It is also observed in many conditions in which there is vasoconstriction or a diminution of the oxygen-carrying capacity of the blood and an impairment of the circulation (Araki). As will be seen later, anhydremia results in a decreased blood volume and an impaired circulation and oxygen-carrying capacity in the blood and vasoconstriction.

The blood often contains an abnormal amount of lactic acid (Clausen). Acetone, diacetic acid and oxybutyric acid may be present, but rarely in excessive amounts (Moore). Despite the fact that large amounts of

organic acid are not found in the blood there are changes which are indicative of a considerable degree of acidosis. There is a diminished alkali reserve, carbon dioxide content and bicarbonate-combining power of the blood. The dried residue of the serum is more acid than normal. There is a decreased oxygen capacity of the hemoglobin and an increased hydrogen ion concentration of the venous blood (Sellards, Howland and Marriott, Ylppö, Schloss and Stetson). The cause of the acidosis will be discussed subsequently.

The blood volume in anhydremia. As a result of the withdrawal of water from the blood the volume necessarily decreases (Rogers, Czerny, Marriott, Utheim, Keith). The reduction in volume may amount to 40 per cent or more of the total and this is due mostly to a decrease in plasma volume (Rogers, Keith). The volume of the blood is rapidly regained when water is administered, provided the anhydremia has been of a slight degree or of short duration, but is only slowly regained when a severe degree of anhydremia has persisted for a considerable time. The blood volume does not return to normal until regeneration of the destroyed cells and protein has taken place or until these constituents have been restored by blood transfusion (Utheim, Keith, Marriott).

The circulatory system in anhydremia. With desiccation of the blood and reduction in its volume there occurs a compensatory constriction of the peripheral arterioles and a greatly decreased volume flow of the blood through certain parts of the body. The changes in the circulation are essentially the same as those occurring in other conditions associated with a diminished blood volume (shock, hemorrhage, etc.). The constriction of the peripheral arterioles leads to a stagnation of the corpuscles in the smaller peripheral vessels. On this account cell counts and hemoglobin determinations made on blood obtained by puncture of the skin are considerably higher than on blood simultaneously obtained from the veins of the same individual. A difference of 25 per cent in the counts between the venous and capillary blood has been observed in the blood counts in the case of infants with severe diarrhea (Marriott, Utheim). These differences are similar to those observed by Cannon, Fraser and Hooper in soldiers suffering from wound shock.

Another effect of diminished blood volume is a greatly decreased volume flow of the blood through the extremities. The flow of blood per unit volume of extremity per minute was found to be less than 10 per cent of the normal flow, in the case of anhydremic infants (Marriott, Utheim). Similar changes in the circulation were observed by Utheim

in rabbits and dogs deprived of water for a considerable time. The measurements of volume flow were made by means of the Stewart calorimetric method, and confirmed in the case of dogs by the use of the Ludwig "Stromuhr." The volume flow of the blood through the extremities increases when the volume of the blood is restored (Marriott, Utheim). It is not known to what extent the volume flow of the blood through the internal organs is diminished. The diminished flow in the extremities would tend to compensate for changes in blood volume and to maintain the circulation through the more vital portions of the body (Gesell).

Disturbances in the cardiac mechanism have been observed by McCulloch in the case of anhydremic infants, the electrocardiograms showing a very low amplitude of all waves, the "T" waves being entirely absent. The P–R interval was increased to as much as 0.20 second, a distinctly prolonged interval for an infant. The Q. R. S. complexes were abnormal in form. Following a restoration of normal blood volume and volume flow the electrocardiograms became normal. This latter finding would support the idea that the cardiac involvement is purely functional and likely the result of an impaired circulation through the coronary vessels. Additional support for this supposition is furnished by the fact that the changes in the electrocardiograms are very similar to those observed in conditions known to be associated with an impaired circulation through the coronary arteries, for example, in coronary sclerosis (McCulloch). This disturbance in the cardiac mechanism may well be a factor in impairing the general circulation.

The pulse becomes small and rapid as anhydremia develops.

The blood pressure is often well maintained, even when a very considerable degree of anhydremia occurs (Feilchenfeld, Utheim, Keith). The increased viscosity of the blood is presumably an important factor in preventing the fall of blood pressure which might otherwise be expected to occur as a result of decreased blood volume. Keith found a normal blood pressure in dogs rapidly dehydrated by saccharose injection, but a lowered blood pressure in animals rendered anhydremic by a prolonged period of abstinence from food and water. It is known that in the latter case the viscosity of the blood is not so high, due to the destruction of blood cells and serum protein (see preceding discussion of composition of the blood in anhydremia). Somewhat lowered blood pressures have been observed by Dennig in man following a restricted water intake. Rogers states that the blood pressure is often very low as the result of anhydremia due to Asiatic cholera.

The urine and renal function in anhydremia. Starling has shown that the secretion of the urine is greatly decreased as the colloidal osmotic pressure of the blood approaches the arterial pressure in the renal arterioles. Such a condition exists when the blood becomes concentrated by water loss, the secretion of urine is, therefore, greatly diminished as the result of anhydremia. There may even be complete anuria. Such urine as is secreted has a high specific gravity, 1040 or above (Bessau, Spiegler).

Traces of albumin and numerous casts are regularly present.

The urine contains small amounts of reducing sugars (Schiff, Langstein and Steinitz, Schloss). It has been shown by Schloss that the sugar of the urine is chiefly glucose, its presence being readily explained as the natural result of the hyperglycemia previously referred to. In addition to glucose, lactose may appear in the case of anhydremic infants (Langstein and Steinitz, Schloss). The excretion of lactose indicates the absorption of unsplit lactose through the intestinal wall. Bessau states that anhydremia leads to an increased permeability of the gastro-intestinal mucosa. There is but little experimental evidence that the increased permeability is due to the anhydremia *per se*.

There is an excess of organic acids in the urine (Utheim, Clausen). The larger part of this acid is insoluble in ether and contains nitrogen. Its exact nature is unknown but in chemical behavior it resembles closely "oxyproteic acid" (Clausen, Utheim). In the ether soluble fraction of the organic acids, a moderate amount of lactic acid is present (Clausen). There is rarely a significant amount of beta-oxybutyric or diacetic acids (Sellards, Howland and Marriott, Schloss and Stetson).

There is evidence of a distinctly impaired functional capacity of the kidney. Mention has already been made of the fact that the blood shows an excess of urea, total non-protein nitrogen and inorganic phosphate. The phenolsulphonephthalein excretion is lower than normal and the Ambard coefficient is high (Schloss and Stetson). The renal insufficiency is not to be explained on the basis of a definite nephritis as the kidney only occasionally shows pathological changes at autopsy (Schloss, Bessau). Furthermore, all evidences of functional renal impairment rapidly disappear with the establishment of a normal water balance. The urine becomes normal in all respects. These facts lead to the conclusion that the renal insufficiency is purely functional and the result of the inability of the kidney to separate a normal urine from a concentrated blood.

The effect of anhydremia on the metabolism. Straub found no increase in the total metabolism of dogs made anhydremic by water deprivation.

Numerous observers have established the fact that anhydremia causes a negative nitrogen balance (Dennig, Straub, Meyer, Landauer, Schiff, Spiegler). This indicates a destruction of body protein.

The mineral salt balance is also negative. There is a loss of sodium, potassium and chloride ions (Meyer, Tobler).

The gastro-intestinal tract. One of the effects of anhydremia is a poor absorption of fat and protein from the gastro-intestinal tract (Dennig, Gürber). When food is given to a badly desiccated animal, vomiting and diarrhea usually occur (Straub, Nobel, Heim and John, King, McGee, Marriott).

Acidosis. Desiccation of the body leads to a considerable degree of acidosis. The blood shows characteristic evidences of acidosis, as has been mentioned above. In addition there is a lowered carbon dioxide tension in the alveolar air (Haldane, Howland and Marriott, Schloss and Stetson), and an increased alkali "tolerance," that is to say, the capacity to ingest large amounts of alkali without changing the reaction of the urine to the alkaline side (Sellards, Howland and Marriott, Schloss and Stetson).

The acidosis is not due to an excessive production of the acetone bodies (Howland and Marriott, Moore, Schloss and Stetson). It is due in part to the acids produced as the result of a diminished volume flow of the blood. It has been shown by Wright and Colebrook, by Gesell and others that a diminished volume flow of the blood leads to an overproduction of acids in the tissues, presumably as the result of suboxidation. Clausen has found two of such acid products in the blood and urine of desiccated animals, namely, lactic acid and an ether-insoluble acid resembling oxyproteic acid. Both of these disappear with the establishment of the normal blood flow.

When the urine secretion is much diminished as the result of anhydremia, there is a retention of acids normally excreted. The predominating acid of the urine is ordinarily acid phosphate. In severe anhydremia a phosphate retention occurs (Howland and Marriott). This retention of acid is an additional factor in the production of acidosis. The acidosis is likely of the same general nature as that occurring as the result of chronic nephritis (Marriott and Howland).

The heat-regulating mechanism. When the blood and tissues become concentrated by water loss the amount of water available for evaporation is diminished and ultimately becomes less than that required for

removal of the heat of metabolism. Fever then occurs. High body temperatures in man (104°F. or over) as the result of restricted fluid intake have been observed by Dennig, Rosenstern, Jurgensen, Von Noorden and Solomon. McGee mentions fever as one of the prominent symptoms of desert thirst. Aron, Friese, Grulee and Bonar and Meyer have observed high temperatures in infants of various ages when receiving less than the usual amounts of water. In these cases no cause for fever other than the restricted fluid intake could be found. The temperature usually fell promptly on the administration of water.

Infants during the first days of life occasionally develop high fever which is lowered by administration of water. Such infants are often receiving but small amounts of fluid and show definite evidences of anhydremia (Holt, Crandall, Müller, Rott, Heller, Bakwin, Schick, Von Reuss). It is possible however that the anhydremia is not the sole cause of fever in these infants (Grulee, Utheim, Von Reuss).

Fever has been observed in animals rendered anhydremic by the administration of salts and sugars (Finkelstein, Heim and John, Peteri, Balcar, Sansum and Woodyatt). Temperatures as high as 125°F. have been observed under such conidtions. There is some question as to whether the fever observed (salt fever) is solely the effect of dehydration.

Czerny observed high body temperatures in cats made anhydremic by exposure to warm dry air.

Miscellaneous manifestations of anhydremia. During the development of anhydremia loss of weight occurs which is more rapid than that observed in any other condition. From 10 to 25 per cent of the body weight may be lost within 1 or 2 days' time. The skin becomes gray, wrinkled and dry and loses its elasticity. A fold produced in the skin flattens out slowly. The surface of the body may become anesthetic. The mucous membranes are dry and lustreless. Salivary secretion ceases. The tongue and lips are shrivelled. In infants the fontanelle is depressed.

The extremities are cold even though the rectal temperature may be high. The respirations are deep and often stertorous. This deep breathing, or "air hunger," is a manifestation of acidosis.

Transient deafness and blindness have been observed. The mental state is one of irritability during the earlier stages of anhydremia, later one of stupor. Terminal convulsions are not infrequent. The nervous symptoms are in part referable to the uremia, the result of impaired renal function.

Excellent descriptions of the symptoms of anhydremia in man resulting from desert thirst are given by King and by McGee.

London states that anhydremia lowers the resistance of the body to infection.

The treatment of anhydremia. Administration of water by mouth in sufficient amounts leads to the prompt disappearance of all the manifestations of anhydremia providing the degree of desiccation is not extreme, and has not lasted long enough to have led to much destruction of the body constituents. In severe anhydremia administration of water by mouth in sufficient amounts is often difficult as vomiting is likely to occur. Water is well absorbed through the skin of certain animals, such as frogs. McGee states that the human skin when desiccated is capable of absorbing water applied externally. Definite proof of this assertion is, however, lacking.

Water introduced by way of the rectum is well absorbed.

Fluid in the form of isotonic salt and glucose solution may be introduced intravenously, subcutaneously or intraperitoneally (Rogers, Blackfan and Maxey).

As there is a loss of mineral salts from the body in anhydremia there is an advantage in giving salts as well as water. It has been found that water is much better retained in the body when salts are given at the same time (Czerny, Heim and John, Rogers, Behrend and Tenzer).

As all of the manifestations of anhydremia including the acidosis rapidly disappear when sufficient fluid is administered it is usually unnecessary to give alkali to combat the acidosis. Administration of sodium bicarbonate may even be harmful on account of its effect on further concentrating the blood and because of the alkalosis which usually occurs as a normal water balance of the body is established following anhydremia. The organic acids are burned and excreted leaving behind the excess of alkali which may be slowly excreted over several days. The excess of sodium bicarbonate in the body occasionally leads to the development of manifestations of tetany (Harrop, Marriott).

When anhydremia has existed for a considerable time so that there is a destruction of blood cells and plasma protein the administration of fluid may fail to restore the blood to its normal volume and as a consequence the volume flow of the blood will remain low for some time. This condition may be remedied by transfusion of whole blood, or to a certain extent, by the injection of solutions containing acacia (White and Erlanger, Gesell, Marriott).

Appendix: The blood and the circulation in conditions closely related to anhydremia. In traumatic shock and in experimental shock brought about by mechanical means or by the injection of histamine or proteoses a decrease in the blood volume occurs (Cannon, Keith, Gasser, Erlanger and Meek, Underhill and Ringer, Underhill and Roth). The concentration of hemoglobin and of red blood cells is markedly increased. The total solids of the blood as a whole are increased but the plasma protein concentration remains approximately normal. There is no actual desiccation of the blood, but a loss of plasma presumably by passage through the vessel walls. A similar concentration of cellular elements of the blood occurs in influenza (Underhill and Ringer). In intestinal obstruction(Whipple and Cooke) and following severe burns of the surface of the body (Underhill) and the inhalation of war gases (Underhill) a similar blood picture is produced. In all of the conditions mentioned there is a decrease in blood volume and changes in the circulation which are essentially the same as those observed in anhydremia. Acidosis, hyperglycemia and an increase in the urea and non-protein nitrogen and lactic acid of the blood have been observed in some of these conditions (Aub and Wu, Cannon, Macleod).

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